Facultad de Ciencias

Departamento de Química Orgánica

Extending the synthetic utility of p-quinols: hetero Michael-type additions and Friedel-Crafts reactions

TESIS DOCTORAL

Carolina García García

Madrid, Diciembre 2014

Facultad de Ciencias

Departamento de Química Orgánica

Memoria presentada por

Carolina García García

para optar al grado de

DOCTORA EN QUÍMICA

DIRECTORES DE LA PRESENTE TESIS DOCTORAL

Dra. M. Carmen Carreño García

Dra. María Ribagorda Lobera

Madrid, Diciembre de 2014

Este trabajo ha sido realizado en el Departamento de Química Orgánica de la Universidad Autónoma de Madrid bajo la dirección de la Dra. Mª del Carmen Carreño y la Dra. María Ribagorda Lobera.

El trabajo se ha llevado a cabo gracias a la financiación del Ministerio de Ciencia e Innovación (Proyecto referencia: CTQ2011-24783) y a la obtención de una Beca de Formación para Personal Investigador (FPI) de la Universidad Autónoma de Madrid.

Durante el tiempo de realización de esta tesis doctoral se ha realizado una estancia de 3 meses en la Universidad de Pensilvania, Filadelfia bajo la dirección del Profesor Gary A. Molander al cual quiero agradecer la oportunidad de haber colaborado en su grupo de investigación.

A mi padre

"La mente que se abre a una idea nunca vuelve a su tamaño original"

Desconocido

List of Abbreviations

In this Ph D memory, the abbreviations used during the manuscript are listed in "*Guidelines for Authors"* (*J*. *Org*. *Chem*. **2013**).

Some different abbreviations have been also used:

DIPEA	Diisopropylethylamine
DMAC	Dimethylacetamide
HMDS	Hexamethyldisilazide
*m*CPBA	3-Chloroperoxybenzoic acid
MS	Molecular Shieves
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
Pin	Pinacolyl
*p*TSA	*p*-Toluenesulfonic acid
MW	Microwave

TABLE OF CONTENTS

1 Introduction and objectives. 19

1.1 General introduction. 19

1.2. Objectives. 29

2. Study of base catalyzed reactions of *p*-quinols with aldehydes and imines. 39

2.1. Introduction and objectives. 39

2.1.1. Synthetic interest of 4-alkyl-4-hydroxy-2,5-cyclohexadienones. 39

Synthesis of 4-alkyl-4-hydroxy-2,5-cyclohexadienones. 40

Stereochemical outcome of 4,4-disubstituted cyclohexadienones in conjugate additions. 46

2.1.2. General aspects of the heteroatom conjugate additions to p-quinols. 48

2.1.3. Precedents in our research group. 58

2.2. Results. 71

2.2.1. Synthesis of starting materials. 71

Synthesis of *p*-quinols. 71

Synthesis of sulfonyl benzaldimines. 72

Synthesis of other imines. 76

2.2.2. Study of base catalyzed reactions of p-quinols with aldehydes. 77

Reactions of *p*-quinols with aromatic aldehydes. 77

Reactions of *p*-quinols with heteroaromatic aldehydes. 88

Reactions of *p*-quinols with aliphatic aldehydes. 91

Structural assignment of dihydrobenzo[*d*][1,3]-dioxol-5(7aH)-ones. 96

Mechanism and stereochemistry for the formation of dihydrobenzodioxolones. 99

2.2.3. Study of the base catalyzed reactions of p-quinols with imines. *105*

Reactions of *p*-quinols with sulfonyl benzaldimines. 105

Structural assignment of tetrahydrobenzo[*d*]oxazolone structures. 114

Structural assignment of tricyclic structures. 116

Mechanism and stereochemistry for the formation of tetrahydrobenzoxazolones and heterotricyclic derivatives. 118

Reactions of *p*-quinols with other imines and ketimines. 121

3. Study of Friedel-Crafts reactions of different heteroaromatic derivatives with *p*-quinols. 127

3.1. Introduction and objectives. 127

3.1.1. General aspects of the carbon nucleophiles conjugate additions to p-quinols. 127

Organometallic and transition metal-catalyzed reactions. 127

Organocatalytic desymmetrization. 135

3.1.2. p-Quinols and heterocyles: synthesis, structures and properties. 140

Conjugate additions of indoles to α,β-unsaturated systems. 141

Indoles bearing a 2,5-cyclohexadienone moiety derivatives. 145

3.1.3. Properties and synthesis of indeno[2,1-b]indoles and benzo[c]carbazoles. .. 147

3.2. Results. 156

3.2.1. Intermolecular Friedel-Crafts reactions of different heteroaromatic derivatives with p-quinols. 156

Synthesis of starting materials. 156

Racemic conjugate addition of heteroaromatic derivatives to *p*-quinols. 158

Enantioselective conjugate addition of indoles to *p*-quinols. 173

3.2.2. Intramolecular Friedel-Crafts reaction of 4-(2-indolylalkyl)quinols. 188

Synthesis of starting materials. 188

Synthesis of *p*-quinol derivatives and their behavior in the FC reaction. 197

Derivatization of FC alkylated and arylated products. 217

4. Conclusions. 223

5. Experimental Part. 231

Chapter 1

Introduction and objectives

1 Introduction and objectives.

1.1 General introduction.

The *p*-quinol (4-alkyl-4-hydroxy-2,5-cyclohexadienone) moiety is frequently present in a great number of natural products with simple or complex structures. Some of them show a wide range of interesting biological properties such as antitumoral[1] and trypanocides[2].

Examples of natural *p*-quinols with simple structures are shown in **Figure 1.1**. Jacaranone was isolated in 1999 from the *Ajuga pasiflora*[3], an endemic plant from Afganistan and Pakistan which has been used against a high number of deseases and infections, and presents a high cytotoxic and antitumoral activity. Glycoside, known as well as Cornoside, has been isolated from different plants such as *Tecota capensis*,[4] *Abeliophyllum distichum*,[5] *Cornelius canadensis*,[6] *Polypremum procumbens*[7] and *Tetrachondra hamiltonii*.[7] Directly related to the glycoderivative was the acetate Hallerone obtained from *Halleria lucida*[8] and *Phyla nodiflora*.[9]

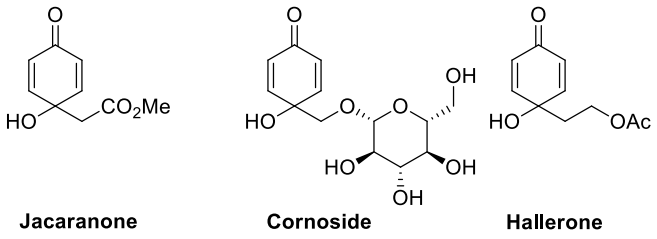


Figure 1.1

---

[1] (a) Massaoka, M. H.; Matsuo, A. L.; Figueiredo, C. R.; Farias, C. F.; Girola, N.; Arruda, D. C.; Scutti, J. A. B.; Romoff, P.; Favero, O. A.; Ferreira, M. J. P.; Lago, J. H. G.; Travassos, L. R. *PLoS One*. **2012**, *7*, 38698, 1; (b) Chew, E.-H.; Lu, J.; Bradshaw, T. D.; Holgren, A. *FASEB J.* **2008**, *22*, 2072; (c) McCarroll, A.; Bradshaw, T. D.; Westwell, A. D.; Matthews, C. S.; Stevens, M. F. G. *J. Med. Chem.* **2007**, *50*, 1707; (d) Berry, J. M.; Bradshaw, T. D.; Fichtner, I.; Ren, R.; Schwalbe, C. H.; Wells, G.; Chew, E.-H.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem*. **2005**, *48*, 639; (e) Bradshaw, T. D.; Matthews, C. S.; Cookson, J.; Chew, E.-H.; Shah, M.; Bailey, K.; Monks, A.; Harris, E.; Westwell, A. D.; Wells, G.; Laughton, C. A.; Stevens, M. F. G. *Cancer Res.* **2005**, *65*, 3911.

[2] Capes, A.; Patterson, S.; Wyllie, S.; Hallyburton, I.; Collie, I. T.; McCarroll, A. J.; Stevens, M. F. G.; Frearson, J. A.; Wyatt, P. G.; Fairlamb, A. H.; Gilbert, I. H. *Bioorg. Med. Chem.* **2012**, *20*, 1607.

[3] Muhammad, P.; Ahmad, S.; Nawaz, H. R.; Ullah, N.; Malik, A. *Fitoterapia* **1999**, *70*, 229.

[4] Guiso, M.; Marra, C.; Piccioni, F.; Nicoletti, M. *Phytochemistry* **1997**, *45*, 193.

[5] Yamamoto, H.; Yoshida, K.; Kondo, Y.; Inoue, K. *Phytochemistry* **1998**, *48*, 273.

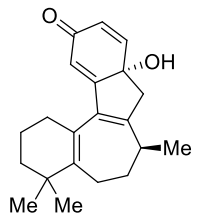
[6] Stermitz, F. R.; Krull, R. E. *Biochemical Systematica and Ecology* **1998**, *26*, 845.

[7] Jensen, S. R. *Biochemical Systematica and Ecology* **2000**, *28*, 45.

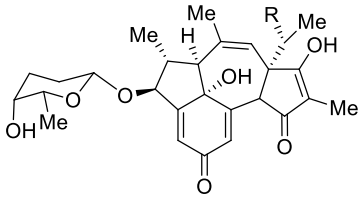
[8] Messana, I.; Sperandei, M.; Multari, G.; Galeffi, C.; Bettolo, G. B. M. *Phytochemistry* **1984**, *11*, 2619.

[9] Ravikanth, V.; Ramesh, P.; Diwan, P. V.; Venkateswarlu, Y. *Biochemical Systematica and Ecology* **2000**, *28*, 905.

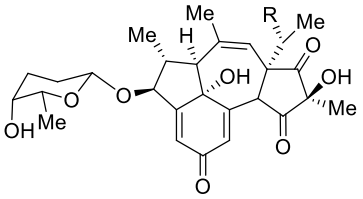
More complex structures having a *p*-quinol moiety found in the world of natural products are represented in **Figure 1.2**. Frondosin C, isolated in 1997 from a marine sponge from the *Dysidea frondosa*[10] family, possesses antiinflamatory and anti-HIV activity.



Frondosin C



Tetrapetalone A (R=H)
Tetrapetalone B (R=OAc)



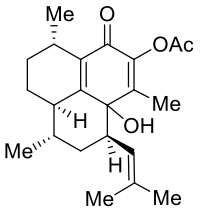
Tetrapetalone C (R=H)
Tetrapetalone D (R=OAc)

Figure 1.2

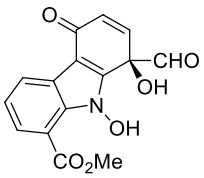
Tetrapetalones A, B, C and D (**Figure 1.2**), were isolated in 2003 by the research group of Hirota from a *Streptomices species*,[11] and present an inhibiting action of the lipooxigenase.

Other natural *p*-quinols with confirmed biological activity are Elisabethol and Coproverdine shown in **Figure 1.3**. Elisabethol was isolated in 2003 from *Pyrrhosoma Elisabethae* and presents antiinflamatory activity.[12] Coproverdine, a marine alkaloid isolated in New Zeland in 2002 from an unknown ascidian, has cytotoxic activity.[13]

[10] Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047.
[11] Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Hirota, A. *Tetrahedron Lett.* **2003**, *44*, 1659.
[12] Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215.
[13] Urban, S.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2002**, *9*, 1371.



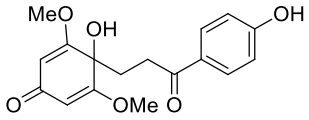
Elisabethol



Coproverdine

Figure 1.3

The natural *p*-quinol Cochinchinenone[14] (**Figure 1.4**), isolated from a red resin of *Dracaena cochinchinensis*, has been recently synthesized by our research group.[15]

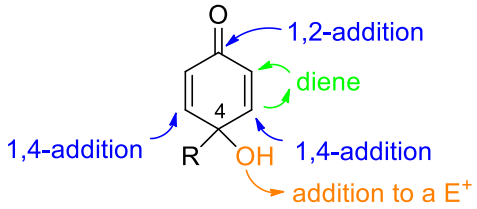


Cochinchinenone

Figure 1.4

From the synthetic point of view, the 2,5-cyclohexadienone motif is very interesting because it can undergo a large array of useful transformations (**Figure 1.5**). Up to two 1,4-additions of nucleophiles to the α,β-conjugated double bonds of the double enone moeity and the 1,2-addition of nucleophiles on the carbonylic carbon can lead to highly functionalized cyclohexane derivatives. Moreover, the conjugated double bonds could act as dienophiles in Diels Alder reactions and the tertiary hydroxyl group at C-4 can behave as nucleophile giving reactions with electrophiles. Thus, the system is ambident since it could react both as electrophile and nucleophile. Additionally, the products of these transformations often retain a synthetic potential, useful for further elaboration. As a result, these molecules are attractive intermediates for natural product synthesis.[16]

[14] Zhu, Y.; Zhang, P.; Yu, H.; Li, J.; Wang, M.-W.; Zhao, W. *J. Nat. Prod.* **2007**, *70*, 1570.
[15] Barradas, S.; Hernández-Torres, G.; Urbano, A.; Carreño, M. C. *Org. Lett*. **2012**, *14*, 5952.
[16] (a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383; (b) Roche, S. P.; Porco, J. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 4068.



4-hydroxy-2,5-cyclohexadienone

Figure 1.5

In spite of their general interests, there are some aspects of the potential synthetic ability of *p*-quinols that remains unexplored.

The conjugate additions on *p*-quinols had been studied using heteroatomic nucleophiles and carbon nucleophiles both in intra and intermolecular manners.[17] Although several examples of oxa- and aza-Michael intramolecular additions to *p*-quinol derivatives had been reported, up to our work, published in 2010, reactions of these systems with aldehydes under Morita-Baylis-Hillman[18] reaction conditions had not been studied.

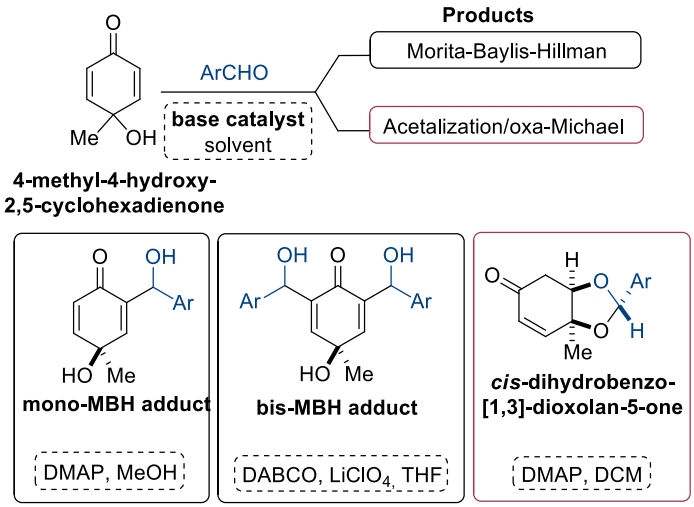
In a precedent work by our research group, directly related with this Ph D Thesis, a study of reactions between 4-methyl-4-hydroxy-2,5-cyclohexadienone and aromatic aldehydes under Morita-Baylis-Hillman reaction conditions was reported.[19] In the presence of different bases, very different structures were formed depending on the chosen experimental parameters. Thus, as represented in **Scheme 1.1**, the use of DMAP (dimethyl aminopyridine) in MeOH afforded mono-MBH adducts while the combination DABCO (1,4-diazabicyclo[2.2.2]octane)/$LiClO_4$ gave the bis adducts. The change of solvent in the DMAP catalyzed process (CH_2Cl_2) afforded byclic-[1,3]-dioxolan-5-one structures with excellent diastereoselectivities as the result of an acetalization/oxa-Michael addition domino process (**Scheme 1.1**).

---

[17] (a) Yang, X.; Wang, J.; Li, P. *Org. Biomol. Chem.* **2014**, *12*, 2499; (b) Kalstabakken, K. A.; Harned, A. M. *Tetrahedron* **2014**, *70*, DOI: 10.1016/j.tet.2014.07.081.

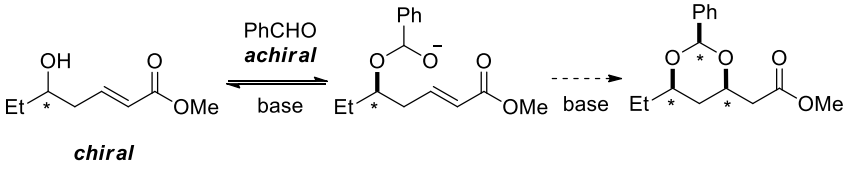
[18] a) Ciganek, E. In Organic Reactions; The catalyzed R-hydroxyalkylation and R-aminoalkylation of activated olefins (The Morita-Baylis-Hillman reaction); L. A. Paquette, Ed.; Wiley: NewYork, **1997**; Vol. 51, p 201; b) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447 and references cited therein; c) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496.

[19] Redondo, M. C.; Ribagorda, M.; Carreño, M. C. *Org. Lett.* **2010**, *12*, 568.



Scheme 1.1

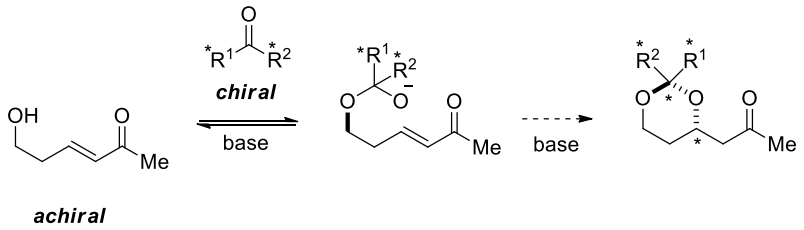
This base catalyzed acetalization/oxa-Michael domino process had been reported on acyclic γ-hydroxy-α,β-unsaturated systems.[20] The stereoselective procedure developed by Evans and Gauchet-Prunet[20a] has been utilized for several natural product syntheses. In this case the newly introduced stereocenter was controlled by the chiral secondary alcohol of starting material (**Scheme 1.2**).



Scheme 1.2

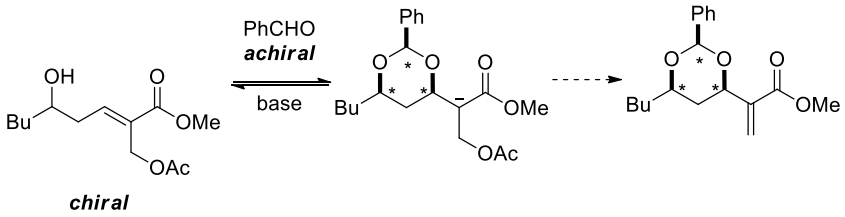
Kitahara[20b] *et al.* developed for the first time an oxa-Michael addition of a chiral ketone or aldehyde to an achiral alcohol affording good ratios of the possible diastereoisomers (**Scheme 1.3**).

[20] a) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446; b) Watanabe, H.; Machida, K. ; Nagatsuka, H. ; Kitahara, T. *Chirality* **2001**, *13*, 379; c) Aouzal, R.; Prunet, *Org. Biomol. Chem*. **2009**, *7*, 3594.



Scheme 1.3

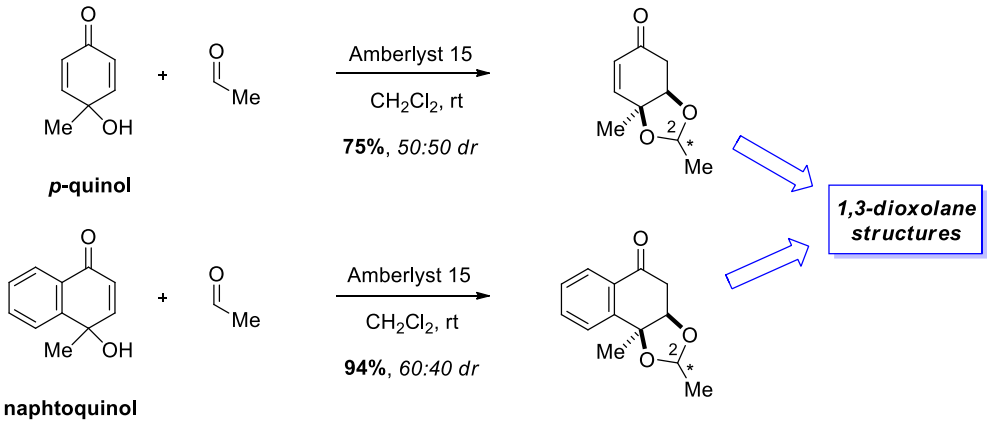
Prunet's research group[20c] developed, in 2009, the synthesis of functionalized Morita–Baylis–Hillman adducts, encompassing a *syn* 1,3-diol protected as a benzylidene acetal, by a new method based on the stereoselective intramolecular conjugate addition of a hemiacetal anion formed *in situ* from a homoallylic alcohol and benzaldehyde in the presence of base, followed in the same pot by elimination of a suitable leaving group (**Scheme 1.4**).



Scheme 1.4

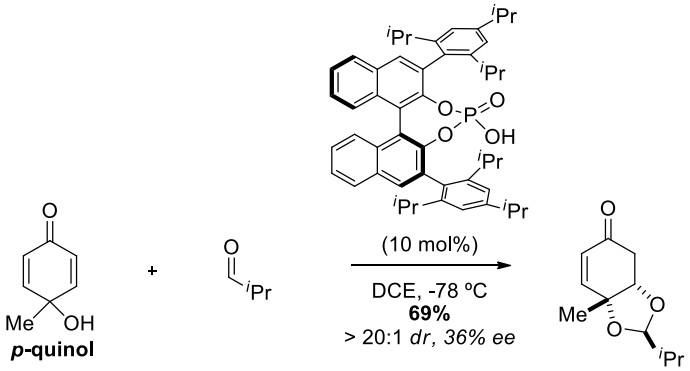
The few examples of the reaction of *p*-quinols with aldehydes or imines described in the literature corresponded to acid catalyzed processes. Jefford *et al.*[21a] reported in 1985 the reaction of *p*-quinols and naphtoquinols with aldehydes in the presence of Amberlyst 15 or H_2SO_4 in aqueous solution. Under these conditions, *cis*-fusionated 1,3-dioxolane derivatives were formed in moderate to good yields but in a poor diastereoselectivity of the C-2 epimers (**Scheme 1.5**).

[21] (a) Jefford, C. W.; Rossier, J. C.; Kohmoto, S.; Boukouvalas, J. *Synthesis* **1985**, 29; (b) Rubush, D. M.; Rovis, T. *Synlett.* **2014**, *25*, 713.



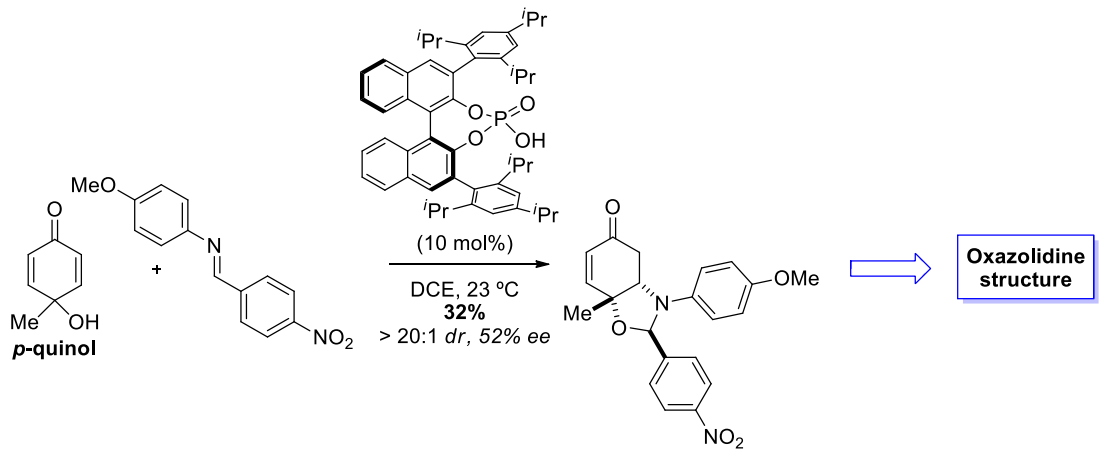
Scheme 1.5

During the preparation of this Ph D work, in 2014, the group of Rovis reported the preparation of the above mentioned 1,3-dioxolanes enantioselectively using an analogue methodology in the presence of an acidic catalyst derived from an enantiopure phosphoric acid.[21b] The acetalization/oxa-Michael desymmetrizarion of *p*-quinol with isobutyraldehyde was achieved in the presence of 10 mol% of a phosphoric acid derived from BINOL under the conditions shown in **Scheme 1.6**. A moderate yield of 69%, > 20:1 of diastereoselectivity and 36% *ee* resulted.



Scheme 1.6

They also reported some examples of the domino hemiaminal formation/aza-Michael reaction occurring when *p*-quinol reacted with an imine in the presence of an enantiopure phosphoric acid as catalyst. The only example of a desymmetrization process in the reaction with an imine afforded only a 32% yield of a oxazolidine derivative in high diastereoselectivity and a 52% of enantiomeric excess (**Scheme 1.7**).

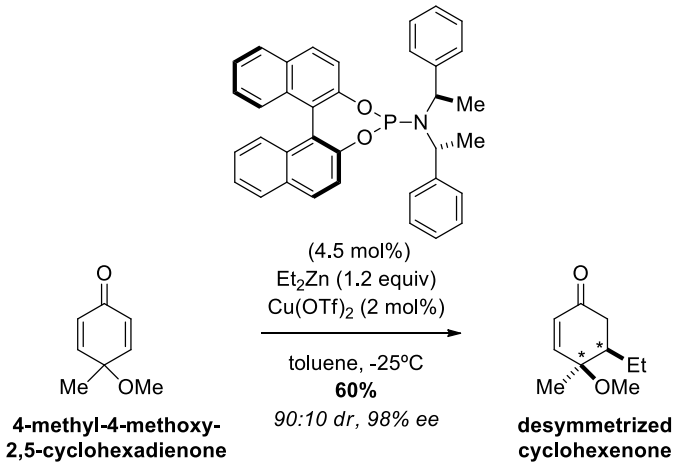


Scheme 1.7

Besides the heteroatom Michael addition reactions other conjugated additions of carbonated nucleophiles to *p*-quinols have been described in the literature.[17] Most of the examples reported of addition to *p*-quinol systems proceeded in an intramolecular manner. There are only a few examples of intermolecular conjugated addition of carbonated nucleophiles to *p*-quinols.

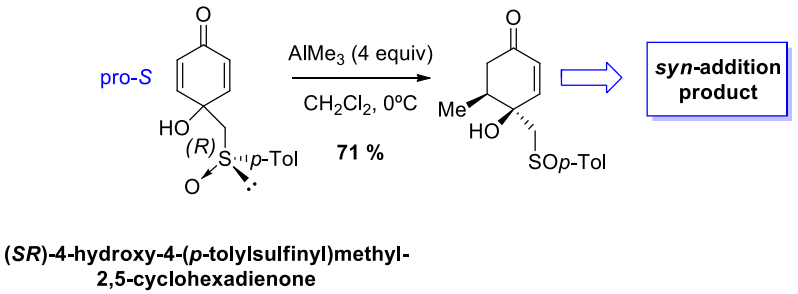
Feringa *et al.*[22] performed in 1999, a series of studies on the asymmetric intermolecular conjugate addition of carbonated nucleophiles to cyclohexadienone derivatives, including *p*-benzoquinone monoketals and *p*-quinols with the OH in the form of methyl ether (**Scheme 1.8**). They performed the addition of dialkylzinc reagents to, for example, 4-methyl-4-methoxy-2,5-cyclohexadienone in the presence of an enantiopure phosphoramidite derived from BINOL to provide desymmetrized cyclohexenones with high levels of enantioselectivity and diastereoselectivity. In the case of 4-methyl-4-methoxy quinol, the *syn* addition product with respect to the methoxy group was formed (**Scheme 1.8**).

[17] (a) Yang, X.; Wang, J.; Li, P. *Org. Biomol. Chem.* **2014**, *12*, 2499; (b) Kalstabakken, K. A.; Harned, A. M. *Tetrahedron* **2014**, *70*, DOI: 10.1016/j.tet.2014.07.081.
[22] Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett*. **1999**, *1*, 623.



Scheme 1.8

Stereoselective intermolecular introduction of carbonated nucleophiles[23] in the conjugated positions of enantiopure (*SR*)-4-hydroxy-4-(*p*-tolylsulfinyl)methyl-2,5-cyclohexadienone was efficiently developed by our research group. Only the *syn* addition product with respect to the hydroxyl group was observed in all cases when an excess of AlR_3 was used as the nucleophile (**Scheme 1.9**).



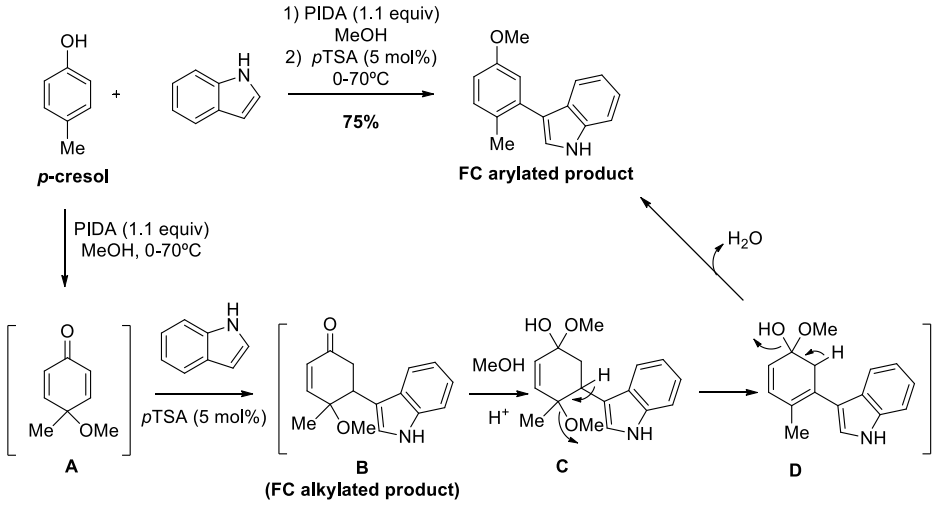
Scheme 1.9

Despite the importance and abundance of indoles[24] in nature and their excellent nucleophility in conjugated addition reactions,[25] there is only one example where indoles

[23] (a) Carreño, M. C.; Pérez-González, M.; Ribagorda, M.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 6758; (b) Carreño, M. C.; Pérez-González, M.; Ribagorda, M.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 3687; (c) Merino, E.; Melo, R. P. A.; Ortega-Guerra, M.; Ribagorda, M.; Carreño, M. C. *J. Org. Chem.* **2009**, *74*, 2824.

[24] (a) Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. Pharmaceutical Substances, Thieme, New York, 4th ed., **2001**. (b) Craig, P. N. Comprehensive Medicinal Chemistry, C. J. Drayton, Pergamon, New York, **1991**, Vol. 8; (c) Negwer, M. Organic Drugs and Their Synonyms: An International Survey, Akademie Verlag, 7th edn., Berlin, **1994**.

behave as a carbonated nucleophile in the intermolecular Michael addition reaction with *p*-quinols, reported by Fan in 2011.[26] As shown in **Scheme 1.10**, the reported work generated the *O*-methyl *p*-quinol *in situ* upon treating *p*-methyl phenol (*p*-cresol) with diacetoxy iodobenzene (PIDA) in MeOH. After 10 min, indole and a catalytic amount of *p*-toluenesulfonic acid (*p*TSA) were added and the initially formed methyl *p*-quinol **intermediate A** acts as an alkylating electrophilic agent of the indole, in a Friedel-Crafts reaction. The resulting Friedel Crafts alkylated **intermediate B**, is first attacked by methanol to form **intermediate C** which undergoes the elimination of methanol affording **intermediate D**, which aromatized by affording the 3-indole substituted 4-methyl *O*-methyl protected phenol (Friedel Crafts arylation product) which was isolated in a 75% yield. As expected, taking into account the π-excedent nature of indole, the FC reaction occurred at C-3 (**Scheme 1.10**).



Scheme 1.10

.

[25] Gribble, G. W. Heterocyclic Scaffolds II: Reactions and Applications of Indoles, Springer, Heidelberg, **2010**, volumen 26, pp 77-88.
[26] Ye, Y.; Wang, H.; Fan, R. *Synlett.* **2011**, *7*, 923.

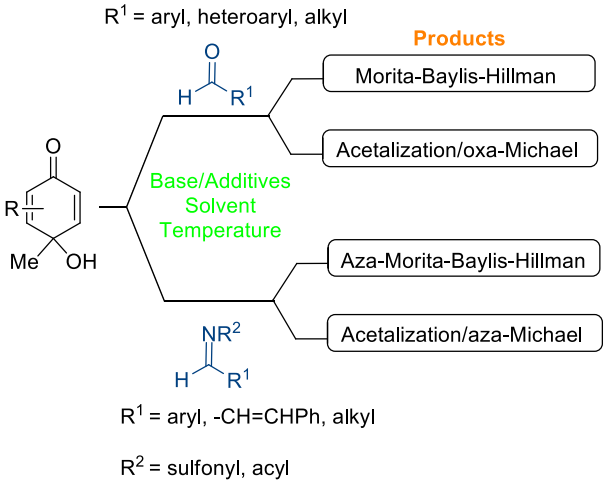
1.2. Objectives.

Considering these precedent results, we decided to focus on two main objectives for the present Ph D work:

1. **Study of base catalyzed reactions of *p*-quinols with aldehydes and imines.**
2. **Study of Friedel-Crafts reactions of different heteroaromatic derivatives with *p*-quinols.**

Study of base catalyzed reactions of *p*-quinols with aldehydes and imines.

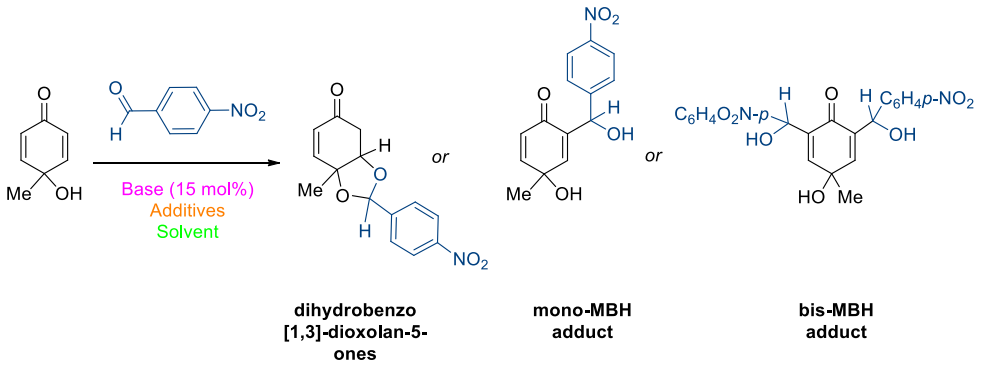
Taking into account the lack of systematic studies devoted to base-catalyzed reactions of *p*-quinols with aldehydes or imines and the initial results obtained in our research group in the MBH reactions of *p*-quinols, the first objective was centered on the base-catalyzed reactions of *p*-quinols with aromatic, heteroaromatic and aliphatic aldehydes and differently *N*-protected aryl, α,β-unsaturated and aliphatic imines in both MBH and acetalization/oxa (aza)-Michael experimental conditions (**Scheme 1.11**).



Scheme 1.11

1.1. Study of base catalyzed reactions of p-quinols with aldehydes.

The main goal of these studies was to look for conditions leading to the major formation of the dihydrobenzodioxolanone derivatives among the different products that had been previously obtained in similar reactions with aromatic aldehydes: Morita-Baylis-Hillman adducts and/or dihydrobenzo[1,3]-dioxolan-5-ones (**Scheme 1.12**).



Scheme 1.12

As summarized in **Scheme 1.12** we were planning to use different bases to catalyze the reactions. The effect of the presence of different additives, change of solvents and/or temperatures on the results was checked. Thus, the optimization, scope and enantioselective version of these base-catalyzed reactions of *p*-quinols will be studied with aromatic, heteroaromatic and aliphatic aldehydes.

The effect of the structure of the aldehydes on the results was also considered. Initially, a model of reactive aldehyde such as *p*-nitrobenzaldehyde, will be studied in order to find the best reaction conditions en route to each product. Afterwards, the effect of the presence of different electron with-drawing groups (EWG) and electron donating groups (EDG) on the aromatic aldehydes will be considered, as well as the use of heteroaromatic aldehydes. The behavior of aliphatic and α,β-unsaturated aldehydes will be also evaluated (**Figure 1.6**). An essential aspect of this study will be the stereochemistry of all the reactions.

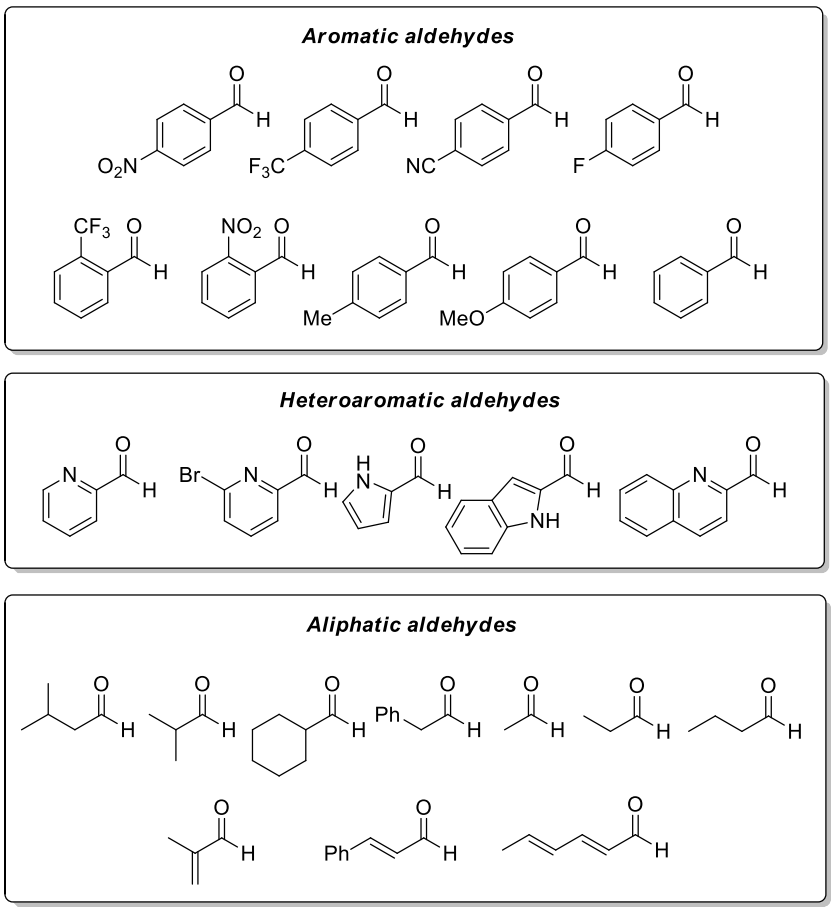
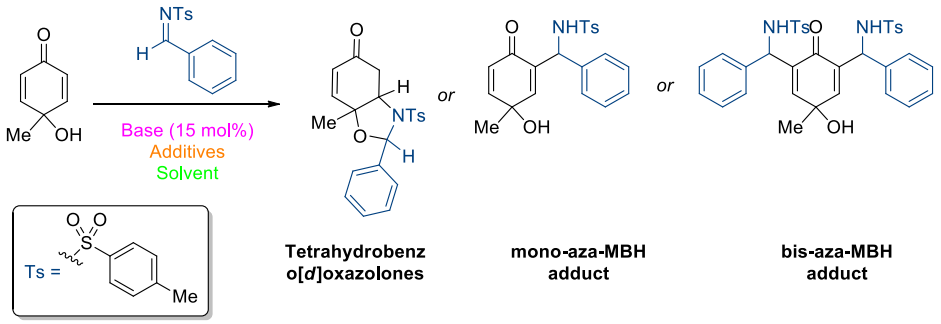


Figure 1.6

1.2. Study of base catalyzed reactions of p-quinols with imines.

Taking into account the few examples of reactions of *p*-quinols with imines previously reported, we decided to focus, as a second objective of this chapter, on the base-catalyzed reactions of *p*-quinols with aldimines under aza-Morita-Baylis-Hillman conditions. In spite of the interest of this reaction, it had not been previously studied with *p*-quinols. Again, a model reaction between *p*-quinol and *p*-toluenesulfonyl benzaldimine (Tosyl benzaldimine) derived from benzaldehyde, will be used to look for the better conditions en route to the different products. An example of a *N*-sulfonyl aldimine was chosen as electrophilic substrate due to its higher stability when compared with other imines. Checking different bases, the presence of additives, different solvents and temperatures we expected to find these adequate conditions to obtain selectively the aza-Morita-Baylis-Hillman adducts and the tetrahydrobenzo[*d*]oxazolones (**Scheme 1.13**).



Scheme 1.13

The effect of substitution both at the aldehyde and at the sulfonyl moeity will be considered in aromatic systems. A few examples of phenyl-α,β-unsaturated imine and aliphatic aldimines keeping the tosyl group at the nitrogen will be also checked. A sulfonyl ketimine will be tried in order to check if the reactivity could be extended to ketones. Finally, the nitrogen protecting group will be change from sulfonyl group to acyl group in order to study its influence in the course of the reaction (**Figure 1.7**).

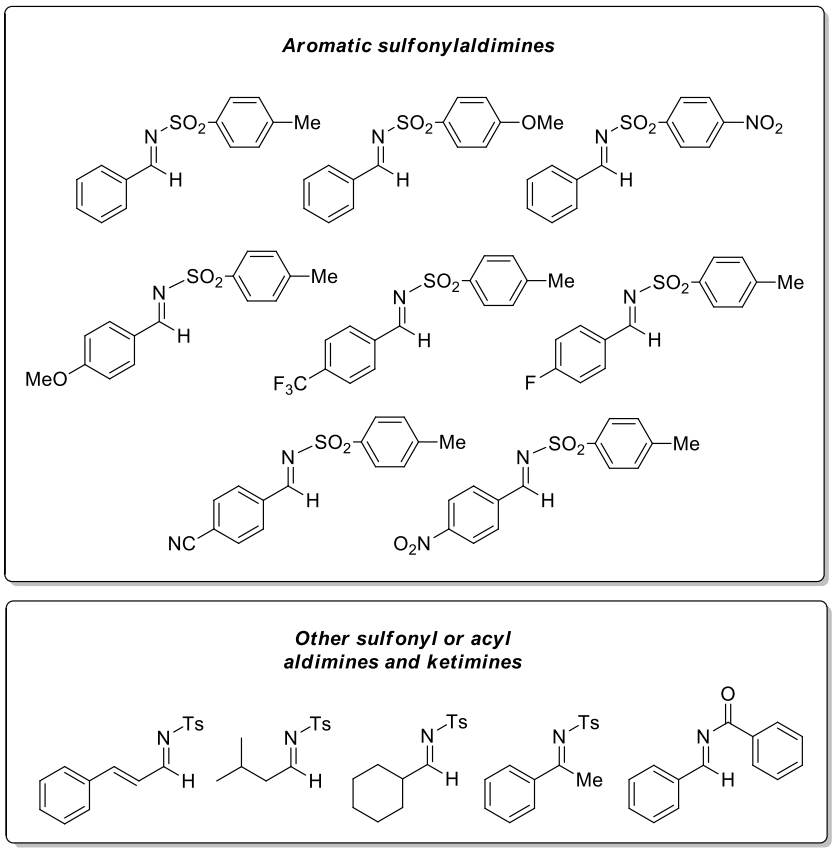


Figure 1.7

Study of Friedel-Crafts reactions of different heteroaromatic derivatives with *p*-quinols.

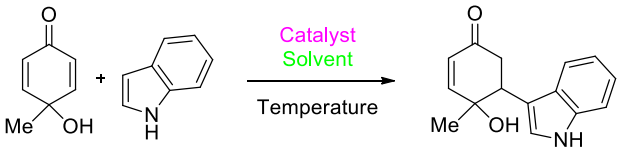
The second main objective of this Ph D Thesis corresponds to the study of the behavior of the 2,5-cyclohexadienone moiety of *p*-quinols as electrophile in Friedel-Crafts alkylations of π-excedent heteroaromatic derivatives. The incorporation of indole or benzofuran fragments into the p-quinol system via 1,4-addition of the π-excedent system to the enone, is of huge interest due to the high synthetic potential of the resulting structures.

The lack of precedent prompted us to carry out a systematic study of these reactions, in order to evaluate their synthetic potential.

Thus, this second chapter is in turn divided in two differentiated parts:

2.1. Intermolecular Friedel-Crafts reactions of different heteroaromatic derivatives with p-quinols.

We initially carry out the reactions summarized in **Scheme 1.14**. A model reaction between 4-methyl-4-hydroxy-2,5-cyclohexadienone and highly reactive 1H-indole was evaluated under different conditions, changing catalysts, solvents and temperature. Finding the best conditions to synthetize the alkylation product was essential to further extend the scope of the procedure.



Scheme 1.14

Later, other heterocyclic derivatives such as pyrrols, furans, tiophens and electron-rich aromatic derivatives will be studied in order to determine the generality of the alkylation process (**Figure 1.8**) as well as differently substituted *p*-quinols (**Figure 1.9**).

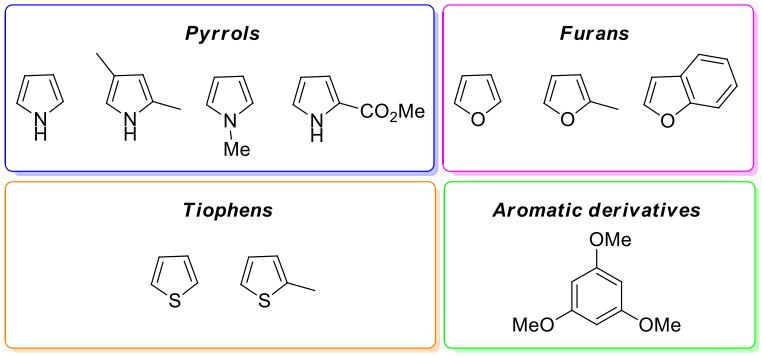


Figure 1.8

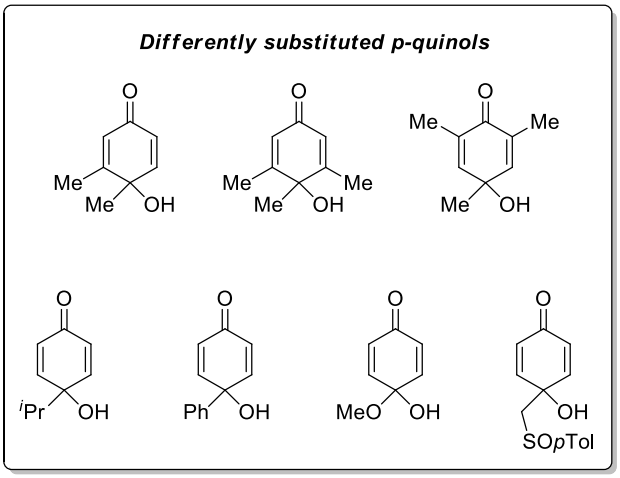
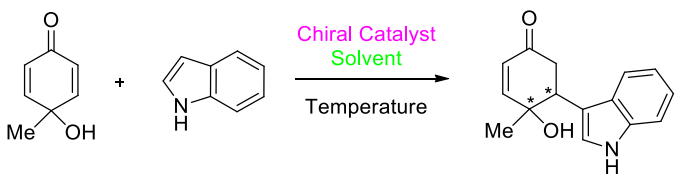


Figure 1.9

Apart from the optimization and scope of the reaction, an essential goal of our work was to develop an enantioselective version. Taking into account all the stereochemical features associated with 1,4-additions to prochiral *p*-quinol, this was not an easy task. The enantioselective study of these reactions was based on the use of asymmetric catalysis in the model reaction previously mentioned for the racemic version of this reaction (**Scheme 1.15**). Once the optimal conditions are established, we will developed a scope in the enantioselective Friedel-Crafts reaction of 4-methyl-4-hydroxy-2,5-cyclohexadienone with differently substituted indoles.



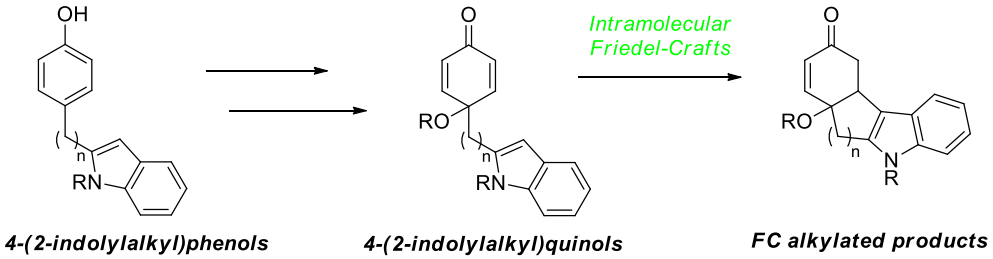
Scheme 1.15

2.2. Intramolecular Friedel-Crafts reactions of 4-(2-indolylalkyl)quinols.

The objective of the second part of this chapter was the study of the intramolecular Friedel-Crafts alkylations of *p*-quinols. In this case, we focused on the potential interest of the tetracyclic systems that could result in these reactions.

As summarized in **Scheme 1.16**, the 4-(2-indolylalkyl)quinols will be submitted to Friedel-Crafts reaction conditions. Initially, the optimized conditions established in Chapter 2.1 will be used.

This study required the synthesis of the indole substituted *p*-quinols. We thus initiate this part of the research with the synthesis of 4-(2-indolylalkyl)phenols, that had not been reported (**Scheme 1.16**).



Scheme 1.16

Chapter 2

Study of base catalyzed reactions of p-quinols with aldehydes and imines

2. Study of base catalyzed reactions of *p*-quinols with aldehydes and imines.

2.1. Introduction and objectives.

2.1.1. Synthetic interest of 4-alkyl-4-hydroxy-2,5-cyclohexadienones.

As mentioned before, apart from being present in the natural world, the 4-alkyl-4-hydroxy substituted cyclohexadienone fragment is important from the synthetic point of view, since it offers a high potential for different transformations.

First of all, cyclohexadienones are easy to synthetize from phenols. This is an important point since such as synthetically versatile class of molecules is easily available in one step from commercially available and inexpensive materials. The double Michael acceptor system present in the *p*-quinol structure acting as electrophile, could lead to highly functionalized systems.[23,27] Moreover, the nucleophilic hydroxy group at C-4 increases the synthetic usefulness of these derivatives which can thus behave as ambident systems.[28] All these structural features make *p*-quinols a unique scaffold to develop domino or multicomponent reactions,[29] for the construction of complex mixtures.

Although these compounds can exist in two isomeric forms: 6-alkyl-6-hydroxy-2,4-cyclohexadienones (*ortho*-quinols) and 4-alkyl-4-hydroxy-2,5-cyclohexadienones (*para*-quinols) (**Figure 2.1**) our research group has mainly focused on the second group, the *p*-quinol derivatives. This choice was based on the instability of *o*-quinols systems due to its propensity to dimerize via [4+2] cycloaddition (**Figure 2.1**). In many cases, this dimerization is so rapid that the monomeric products cannot be isolated. In contrast, 4-alkyl-4-hydroxy-2,5-

---

[23] (a) Carreño, M. C.; Pérez-González, M.; Ribagorda, M.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 6758; (b) Carreño, M. C.; Pérez-González, M.; Ribagorda, M.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 3687; (c) Merino, E.; Melo, R. P. A.; Ortega-Guerra, M.; Ribagorda, M.; Carreño, M. C. *J. Org. Chem.* **2009**, *74*, 2824.

[27] For synthetic applications of *p*-[(*p*-tolylsulfinyl)methyl]-*p*-quinols see: (a) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Org. Lett.* **2005**, *7*, 1419; (b) Carreño, M. C.; Somoza, A.; Ribagorda, M.; Urbano, A. *Chem. Eur. J.* **2007**, *13*, 879; (c) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Chem. Eur. J.* **2007**, *13*, 1064; (d) For a recent overview see: Carreño, M. C.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Comm.* **2009**, 6129.

[28] (a) Carreño, M. C.; García Luzón, C.; Ribagorda, M. *Chem. Eur. J.* **2002**, *8*, 208; (b) Carreño, M. C.; Ribagorda. M. *Org. Lett.* **2003**, *5*, 2425.

[29] (a) Walji, A. M.; MacMillan, D. W. C. *Synlett.* **2007**, 1477; (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; (c) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693; (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem*. **2010**, *2*, 167.

cyclohexadienones are usually isolable and generally stable over the time periods required for use as synthetic intermediates.

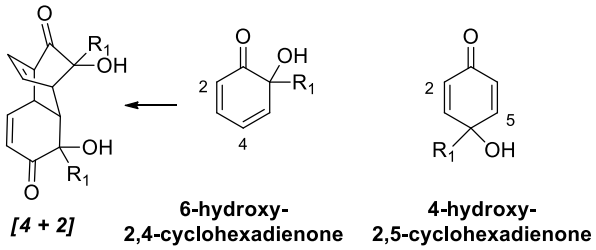


Figure 2.1

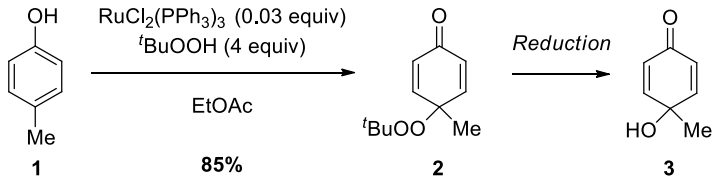
An essential point arising when dealing with synthetic applications of *p*-quinols is the control of the stereochemistry of their reactions. Apart from the prochiral nature of C-4 on symmetric systems, two enantiotopic double bonds are present whose evolution in turn, can occur from two diastereotopic faces. The synthetic utility of these systems is thus limited to a controlled stereochemical evolution.

Synthesis of 4-alkyl-4-hydroxy-2,5-cyclohexadienones.

An important advantage for the use of *p*-quinols in synthesis is their availability. The most straightforward synthetic route to 4-alkyl-4-hydroxy-2,5-cyclohexadienones is through the direct oxidative dearomatization of *p*-alkyl substituted phenols. There are several procedures to accomplish this transformation. Oxidation of *p*-alkyl substituted phenols to *p*-quinols can be achieved using ^{t}BuOOH in the presence of transition metal complexes.[30] In the example shown in **Scheme 2.1**, the ^{t}buthyl peroxy-*p*-quinol **2** resulted upon treatment of *p*-alkylphenol **1** with ^{t}BuOOH using $RuCl_2(PPh_3)_3$ as catalyst. The resulting peroxide **2** could be transformed into the *p*-quinol **3** by means of a reduction process.

[30] (a) Bacon, R. G. R.; Kuan, L. C. *Tetrahedron Lett.* **1971**, *12*, 3397; (b) Hayashi, Y.; Shioi, S.; Togami, M.; Sakan, T. *Chem. Lett.* **1973**, *2*, 651; (c) Schwartz, M. A.; Rose, B. F.; Holton, R. A.; Scott, S. W.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1977**, *99*, 2571; (d) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1983**, *24*, 5611; (e) Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 2210; (f) Krauss, A.; Taylor, W. *Aust. J. Chem.* **1991**, *44*, 1307; (g) Krauss, A.; Taylor, W. *Aust. J. Chem.* **1992**, *45*, 925; (h) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Noda, S. *J. Am. Chem. Soc.* **1996**, *118*, 2509.

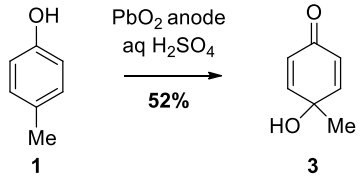
Transition metal complex-catalysed oxydation of p-alkylphenols



Scheme 2.1

The anodic oxidation[31] of *p*-methylphenol **1** using PbO_2 as anode in an acidic solution of H_2SO_4 afforded only 52% yield of *p*-quinol **3**, maybe due to the huge amounts of solvent used in electrochemical processes (**Scheme 2.2**).

Anodic oxydation of p-alkylphenols

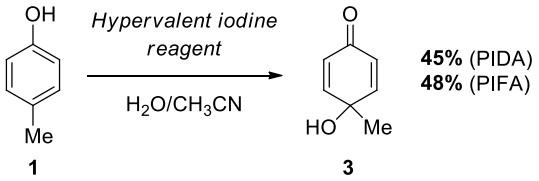


Scheme 2.2

More recently, the use of hypervalent iodine reagents has become a popular approach to *p*-quinols due to the commercial availability of reagents such as PIDA (Phenyliodine diacetate) or PIFA (Phenyliodine bis(trifluoroacetate).[32] Thus, as depicted in **Scheme 2.3**, treatment of *p*-methylphenol **1** with PIDA or PIFA in the presence of water allowed the direct formation of *p*-quinol **3** in moderate yields.

[31] (a) Parker, V. D.; Ronlán, A. *J. Electroanal. Chem. Interfacial Electrochem.* **1971**, *30*, 502; (b) Ronlán, A.; Parker, V. D. *J. Chem. Soc. C Org.* **1971**, 3214; (c) Nilsson, A.; Ronlán, A.; Parker, V. *J. Chem. Soc. [Perkin 1]* **1973**, 2337.

[32] (a) Lewis, N.; Wallbank, P. *Synthesis* **1987**, *1987*, 1103; (b) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677; (c) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435; (d) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc. [Perkin 1]* **1993**, 1891; (e) McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc. [Perkin 1]* **1994**, 2047; (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523; (g) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 6193; (h) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299; (i) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235.



Scheme 2.3

These hypervalent iodine reagents switch the reactivity of phenols from being nucleophiles into becoming electrophiles, which is known as phenolic "umpolung".[33] They are characterized by their electrophility (required for the nucleophilic attack of the corresponding phenol to the iodine center) and their nucleofugality (required for the two-electron transfer from the phenol to the iodine (III) center, which transforms into a monovalent iodine specie and affords the final oxidative dearomatization of the phenol). As depicted in **Scheme 2.4**, the mechanism of this oxidation is initiated by activation of the phenolic OH, which reacts with PIDA or PIFA through the nucleophilic hydroxyl group affording the replacement of a $^{-}$OCOR molecule of the hypervalent iodine reagent. Once the activated phenoxy-iodine (III) **intermediate A** is formed, the reaction progress can undergo three different mechanisms, all of them under the influence of the nucleofugality of the monovalent iodine (iodobenzene) resulting in the 2-electron reduction progress of the iodine (III) specie. Other factors such as the type of solvent (polar, apolar, coordinative,…), the nature of the ligands or the regiochemistry and electronic properties of the substituents on the phenol ring, can define the type of oxidative dearomatization mechanism.

A dissociative mechanism could be proposed due to the observed "hypernucleofugality" of the phenyl-λ^3-iodanyl group. A phenoxenium (PhO^+) **intermediate B** would be formed which could be stabilized by coordinative polar solvents such as alcohols.

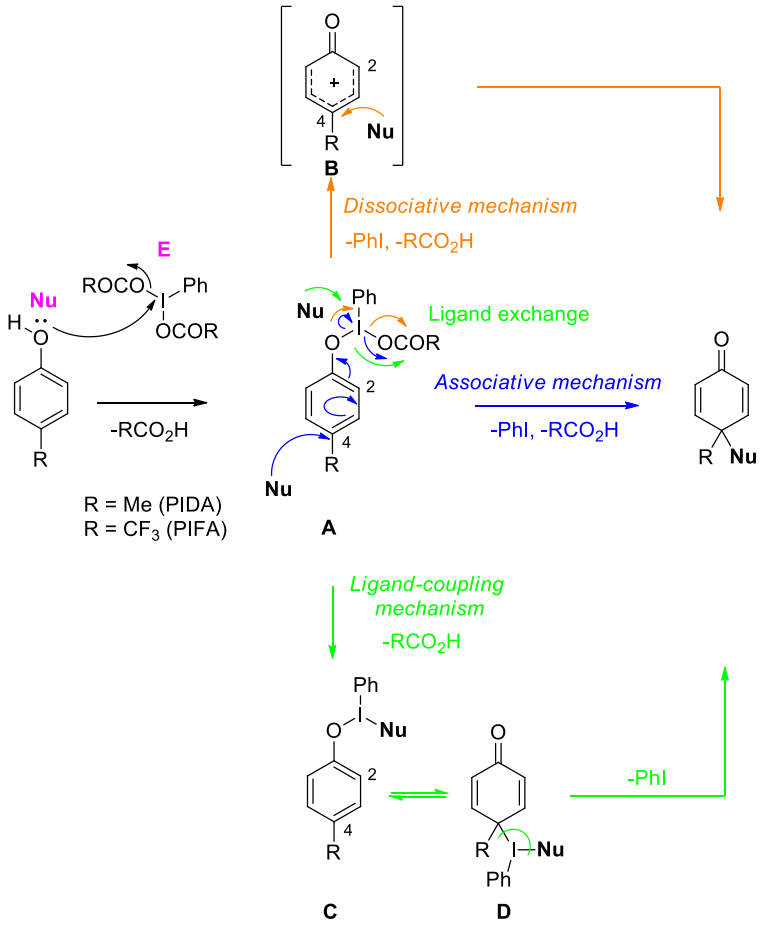
An associative bimolecular mechanism could be also proposed where the attack of the nucleophile (in this case H_2O) occurs in a concertated manner with the departure of the iodobenzene. In this case, a phenoxenium intermediate could be discarded.

Finally, if the nucleophile undergoes a second ligand exchange in the phenoxy-iodine (III) **intermediate A**, the possible tautomers (phenoxy-λ^3-iodane (**intermediate**

[33] (a) Bérard, D.; Giroux, M.-A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, *64*, 7537; (b) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett*. **2008**, *10*, 4629; (c) Sabot, C.; Commare, B.; Duceppe, M.-A.; Nahi, S.; Guérard, K. C.; Canesi, S. *Synlett*. **2008**, 3226; (d) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem*. **2009**, *74*, 2039; (e) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun*. **2009**, 2941.

C)/cyclohexadienonyl- λ^3-iodane (**intermediate D**)) could evolve through a reductive elimination of iodobenzene with the corresponding bond formation between the other two iodine ligands (nucleophile and one of the tautomers), as in the case of the transition metal cross coupling reactions, following the ligand-coupling mechanism.

In all cases, the attack of the nucleophile specie could occur in both positions, 2- and 4- of the phenolic ring, although in this case the attack to the C-2 is not represented.

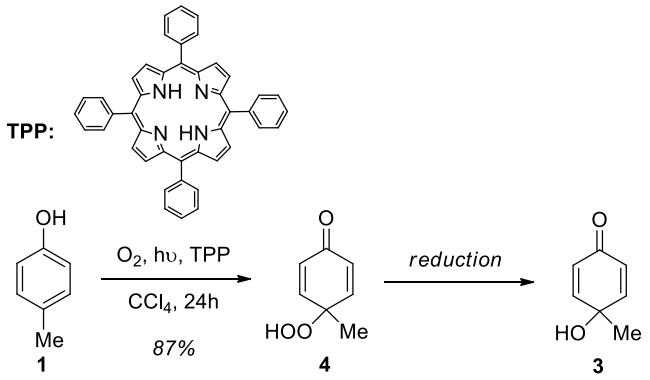


Scheme 2.4

Singlet oxygen has been already employed to synthetize these derivatives.[34] The production of singlet oxygen ($^1O_2$) could be accomplished by using O_2 and a photosensitizer in the presence of light. An example of this methodology, developed by the group of Adam in

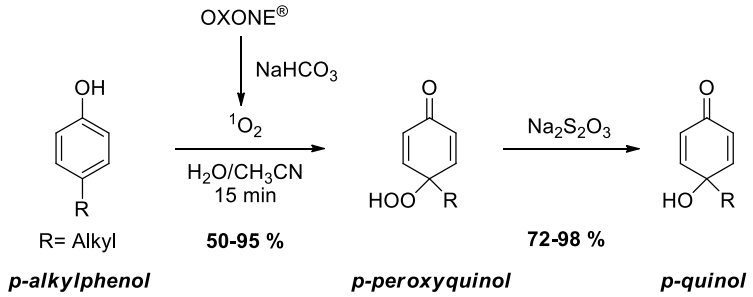
[34] (a) Matsuura, T.; Omura, K.; Nakashima, R. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1358; (b) Endo, K.; Seya, K.; Hikino, H. *Tetrahedron* **1989**, *45*, 3673.

1988,[35] is the use of TPP (5,10,15,20-tetraphenyl-21H,23H-porphyrin) as photosensitizer in the synthesis of *p*-hydroperoxyquinols **4** whose transformation into the corresponding *p*-quinols **3** is accomplished by reduction of these hydroperoxyderivatives (**Scheme 2.5**).



Scheme 2.5

Recently, the use of a mixture Oxone®/$NaHCO_3$ has been developed by our research group for the production of $^1O_2$ and applied to the synthesis of *p*-quinols from *p*-alkylphenols in excellent yields (**Scheme 2.6**).[36]



Scheme 2.6

Oxone® is an inexpensive and easily handled solid consisting of a 2:1:1 mixture of $KOSO_2OOH$, $KHSO_4$, and K_2SO_4. As a result of its nontoxic "green" nature, affordability, and safety profile, Oxone® is nowadays a popular reagent mainly used to synthetize dioxiranes[37]

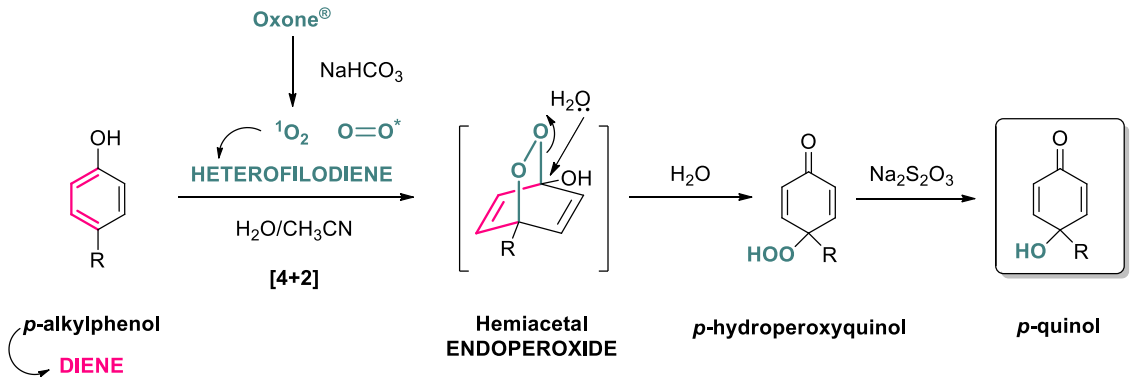
[35] (a) Adam, W.; Kiliç, H.; Saha-Möller, C. R. *Synlett*. **2002**, 510; (b) Prein, M.; Maurer, M.; Peters, E. M.; Peters, K.; von Schnering, H. G.; Adam, W. *Chem. Eur. J.* **1995**, *1*, 89; (c) Adam, W.; Lupón, P. *Chem. Ber.* **1988**, *121*, 21.

[36] Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 2737.

[37] (a) Wong, O. A.; Wang, B.; Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 6335; (b) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093; (c) Ager, D. J.; Anderson, K.; Oblinger, E.; Shi, Y.; VanderRoest, J. *Org. Process Res. Dev.* **2007**, *11*, 44.

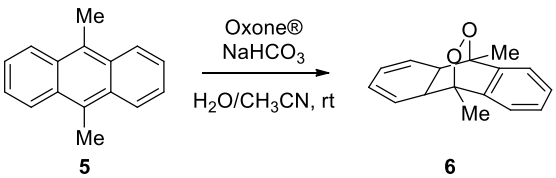
but also applied to the synthesis of *p*-quinols. Initially, under the conditions shown in **Scheme 2.6**, a *p*-hydroperoxide was formed that could be either isolated or reduced by adding a solution of $Na_2S_2O_3$ to the *p*-quinol. Both reactions can be effected sequentially without isolation of the hydroperoxide.

The mechanism explaining the formation of the *p*-quinols from *p*-alkylphenols from Oxone® involves the initial formation of singlet oxygen by decomposition of the reagent in the presence of $NaHCO_3$.[38] A [4+2] cycloaddition then occurs between $^1O_2$ and the electron-rich *p*-alkyl phenol giving rise, initially, to the formation of a 1,4-endoperoxide, which immediately evolves to the 4-alkyl-4-hydroperoxy-2,5-cyclohexadienone as a result of its unstable peroxyhemiacetal structure. The presence of water seems to be essential for the success of this process. Then, the intermediate *p*-hydroperoxyquinol is transformed into the *p*-quinol by reduction with $Na_2S_2O_3$ (**Scheme 2.7**).



Scheme 2.7

This mechanism was supported[39] by the isolation of the stable cyclic endoperoxide **6** when the reaction was effected with 9,10-dimethylanthracene **5** (**Scheme 2.8**).

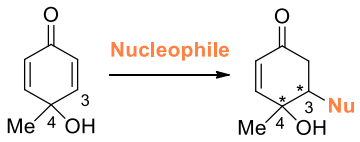


Scheme 2.8

[38] Ball, D. L.; Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1125.
[39] a) Kotani, H.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004**, *126*, 15999; b) Donkers, R. L.; Workentin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1688.

Stereochemical outcome of 4,4-disubstituted cyclohexadienones in conjugate additions.

The synthetic importance of *p*-quinols is due not only to their ambivalent nature but also to the good stereocontrol which can be achieved in their reactions. In the literature, most synthetic targets are chiral and generally exist as a single enantiomer. Thus, the development of synthetic methodologies that provide enantioenriched products has been a priority in last decades. In the case of symmetrically substituted cyclohexadienones, the enantioselective desymmetrization[40] could be one methodology to obtain enantioenriched structures. It would involve the differentiation of two enantiotopic functional groups (in this case, the two enone moieties) through selective reactivity, thus breaking the symmetry of the molecule in a enantioselective manner. Due to the presence of the prochiral center at C-4 in symmetrical *p*-quinols, conjugate additions generate two stereocenters at C-3 and C-4 (**Scheme 2.9**). Therefore, up to four possible stereoisomers could be formed in such processes.



Scheme 2.9

When dealing with such cyclohexadienone derivatives, two stereochemical aspects should be considered in the conjugate addition of nucleophiles or cycloadditions: the double bond selectivity (pro-*R* and pro-*S* β-carbons, **Figure 2.2**) and the face selectivity, since the approaching reagent could attack from the *re* face or *si* face of each one of the double bonds (see in **Figure 2.2** top or bottom nucleophile attack) to give two possible diastereoisomers, in racemic series (four stereoisomers in total).

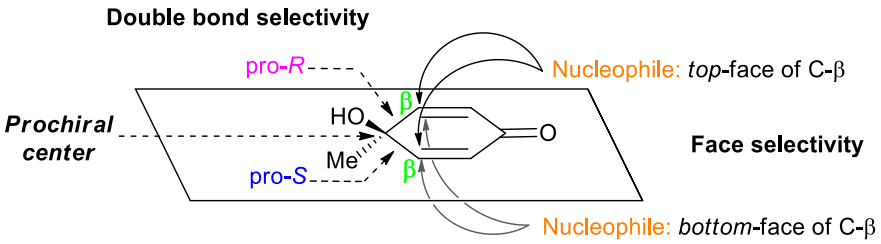
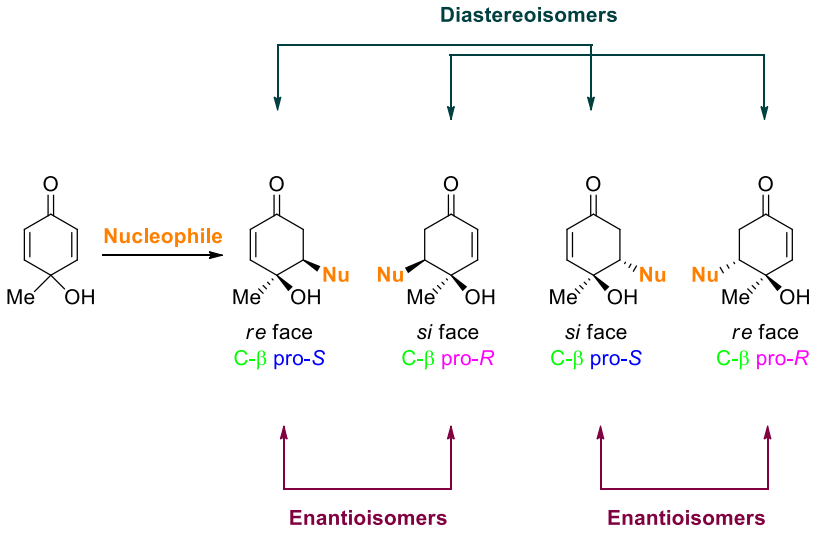


Figure 2.2

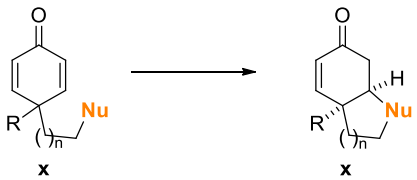
[40] (a) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167; (b) Willis, M. C. *J. Chem. Soc. [Perkin Trans 1]* **1999**, 1765.

Once the nucleophilic attack has occured on one of the β-carbon of the 2,5-cyclohexadienone, 4 stereoisomers can be formed (**Scheme 2.10**): two enantioisomers of the diastereoisomer resulting when the nucleophile attacks by the same face of the hydroxyl group at C-4 and the two enantioisomers of the diastereoisomer formed when the attack occurs by the face containing of the methyl group at C-4.



Scheme 2.10

The control of both diastereo and enantioselectivity by designing a chiral catalyst of ligand is challenging. In order to decrease this issue, there is a common approach consisting in using substrates with an inherent diastereoselectivity, such as those which can undergo a cyclization reaction that preferentially forms a *cis*-fused bicyclic system (**Scheme 2.11**). In this case, only the enantioselective aspect of the problem remains.

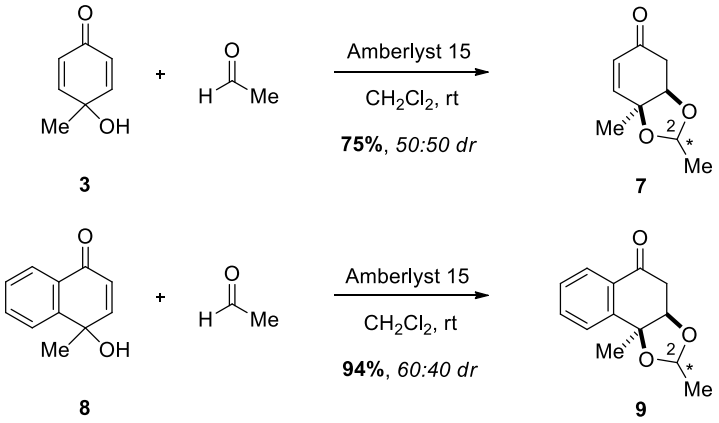


Scheme 2.11

2.1.2. General aspects of the heteroatom conjugate additions to p-quinols.

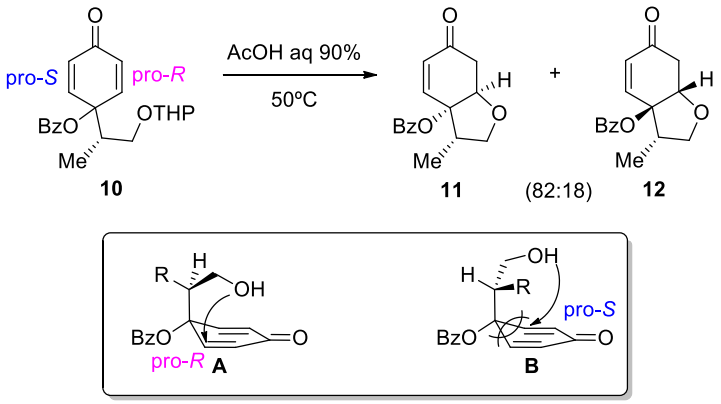
The conjugate additions on *p*-quinols have been studied using heteroatomic nucleophiles and carbon nucleophiles, both in intra or intermolecular manners. The intramolecular hetero-Michael addition of adequately substituted *p*-quinols provides bicyclic derivatives. Precedent work related with heteroatom conjugate addition involving achiral cyclohexadienones as substrates will be commented in this section.[17]

Starting with intramolecular processes, a precedent directly related with the work of this Ph D corresponds to the reaction of *p*-quinols and *p*-naphtoquinols with an aldehyde in the presence of Amberslyst or H_2SO_4 as catalysts, developed by Jefford *et. al.* in 1985.[21a] In this acid catalyzed reaction, the synthesis of bicyclic [1,3]-dioxolanes **7** and **9** was achieved in a racemic manner. Formation of the heterobicyclic derivatives was a consequence of an acetalization/oxa-Michael domino process. The results they obtained evidenced moderate to excellent yields for the formation of dioxolanes but poor diastereoselectivities using either Amberlyst 15 in CH_2Cl_2 or H_2SO_4 in THF at room temperature were obtained (**Scheme 2.12**).



Scheme 2.12

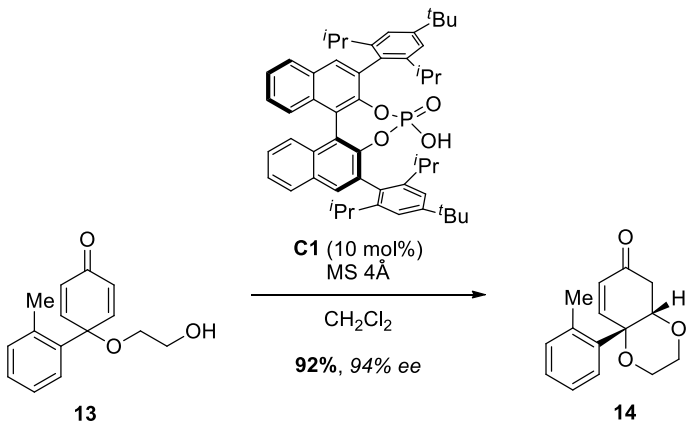
The first enantioselective example reported corresponds to the synthesis of hydrobenzofurans through an intramolecular oxa-Michael reaction of enantiopure *p*-quinol 10 to afford compounds **11** and **12** in 82:18 diastereomeric ratio (**Scheme 2.13**).[41] In this work the differentiation between the two diastereotopic double bonds was observed. The authors explained that the observed pro-*R* double bond selectivity is due to the relative stability of reactive conformer A reacting from the pro-*R* double bond when compared with conformer B attacking the pro-*S* double bond, as the result of the rotation around the C-C exocyclic bond (**Scheme 2.13**). Both reactive rotamers situate the benzoyl group in an equatorial position. Thus, **A** situating the R group far away from the cyclic fragment, is favored with respect to **B**, where the R group is close to the cyclic enone, in a sterically congested disposition, so the attack must be favored by the pro-*R* double bond.



Scheme 2.13

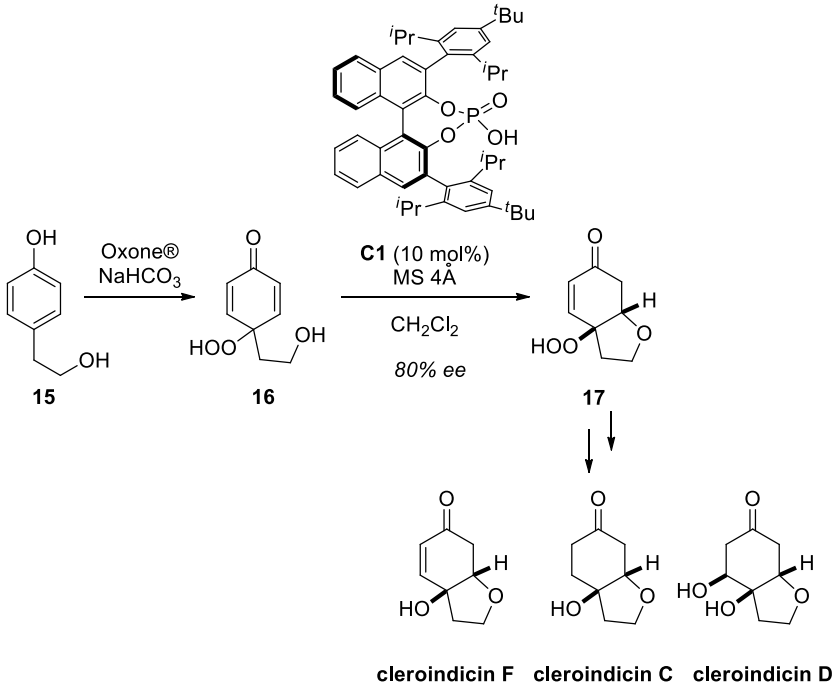
You and coworkers[42] reported, in 2010, the Brønsted acid-catalyzed intramolecular oxa-Michael desymmetrization of 4,4-disubstituted cyclohexadienones derivatives **13** bearing a nucleophilic OH group**.** The formation of the *cis*-fused bicyclic dioxane derivatives **14** in the presence of a catalytic amount of enantiopure phosphoric acid **C1** proceeded in good yields with high levels of stereocontrol (**Scheme 2.14**). In the example shown in **Scheme 2.14**, an aryl group is present at C-4 of the cyclohexadienone leading to a 94% *ee*. The use of alkyl groups instead of the aryl was also studied. Alkyl substituents larger than methyl resulted in decreased enantioselectivity (Me: 94% *ee*, Et: 78% *ee*, ^{i}Pr: 60% *ee*).

[41] Fujioka, H.; Kitagaki, S.; Ohno, N.; Kitagawa, H.; Kita, Y.; Matsumoto, K. *Tetrahedron: Asymmetry* **1994**, *5*, 333.
[42] Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056.



Scheme 2.14

The utility of this methodology was demonstrated in the synthesis of cleroindicins C, D, and F, starting from hydroperoxide **16**, in turn accessible by oxidation via decomposition of Oxone® in the presence of $NaHCO_3$ of *p*-alkylphenol **15** (**Scheme 2.15**).

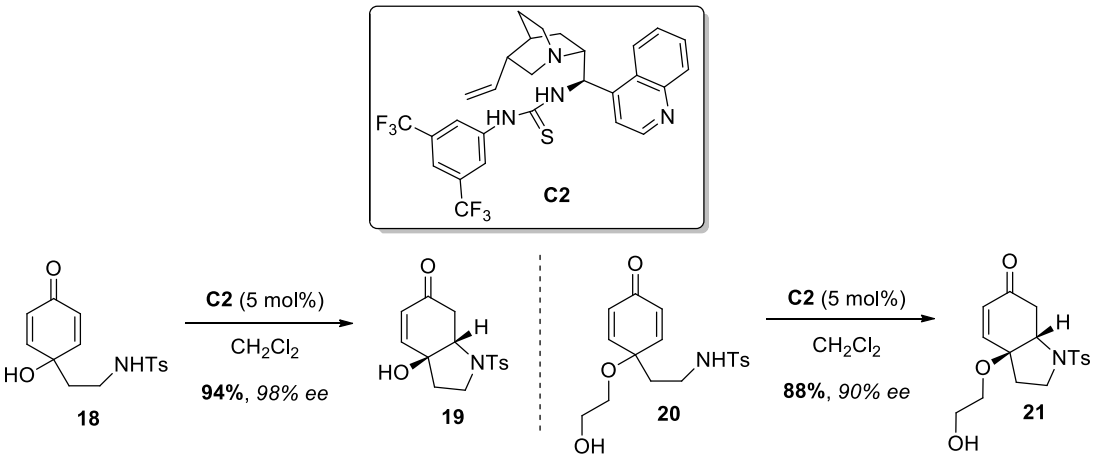


Scheme 2.15

In a different study, this research group described an intramolecular aza-Michael addition catalyzed by *Cinchona* alkaloid-derived thioureas.[43] As shown in the example of **Scheme 2.16**, the cyclization of sulfonamide-tethered cyclohexadienone protected amine **18**

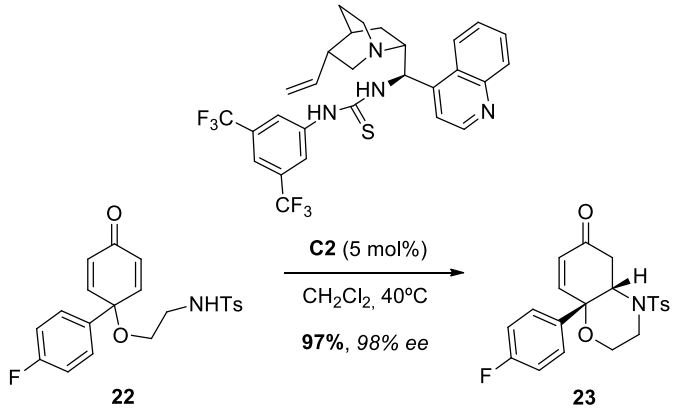
[43] Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519.

was promoted by catalyst **C2**, providing hydroindolones **19**. It was observed that the nitrogen protecting group had great effect on both reactivity and enantioselectivity (Ts: 94% yield, 98% *ee*, Ms: 26% yield, 80% *ee* and Ns: 75% yield, 94% *ee*). Good yields and high levels of enantioselectivity were obtained with *N*-tosyl-substituted cyclohexadienones bearing at C-4 ethers (OMe, OEt), esthers (OAc), aryl groups (3,4-$(MeO)_2C_6H_3$ or even an acetamide substituent (NHAc). Interestingly, substrate **20**, capable of undergoing both the oxa-Michael and aza-Michael addition, preferentially cyclizes through sulfonamide addition affording derivative **21** in 88% yield and 90% *ee* (**Scheme 2.16**).



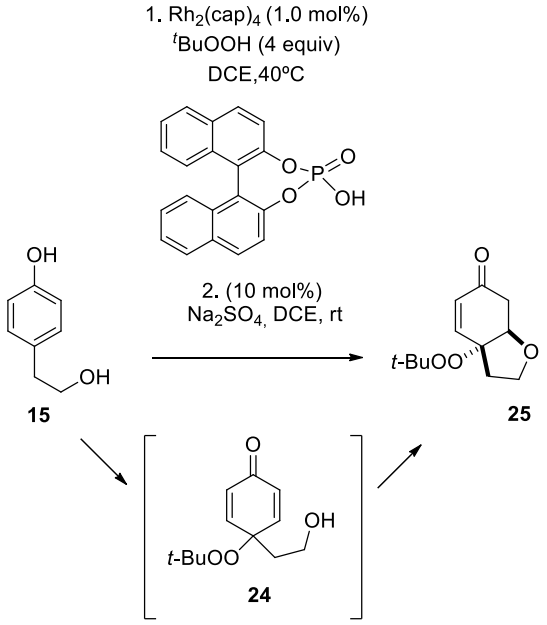
Scheme 2.16

The synthesis of morpholine derivatives **23** was also achieved by cyclization of oxygen-tethered substrates **22** in the conditions described above (**Scheme 2.17**). High yields and enantiomeric ratios were obtained for most 4-aryl substituted and 4-alkyl substituted substrates but both decrease when bulky alkyl substituents are used instead (Me: 96% yield, 96% *ee*, Et: 97% yield, 96% *ee*, ^{i}Pr: 73% yield, 94% *ee*, ^{t}Bu: no reaction).



Scheme 2.17

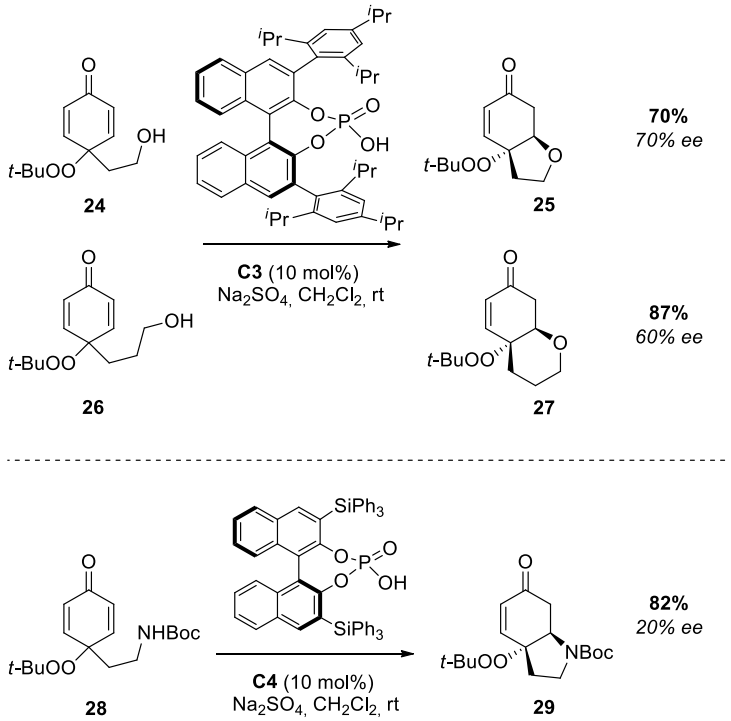
More recently, a procedure furnishing oxo- and aza-heterocycles from functionalized *p*-alkylphenols was reported by Doyle and coworkers.[44] A tandem phenol oxidation-Michael addition process using dirhodium caprolactamate [$Rh_2(cap)_4$] as the catalyst in the oxidation of *p*-alkylphenol by ^{t}BuOOH (affording **24** *in situ*) and a Brønsted acid as the catalyst in the oxa- or aza-Michael reaction was achieved in moderate to good yields. As an example of the tandem process, bicycle **25** was obtained in 62% isolated yield from *p*-alkylphenol **15** using the catalytic system described in **Scheme 2.18**.



Scheme 2.18

[44] Ratnikov, M. O.; Farkas, L. E.; Doyle, M. P. *J. Org. Chem.* **2012**, *77*, 10294.

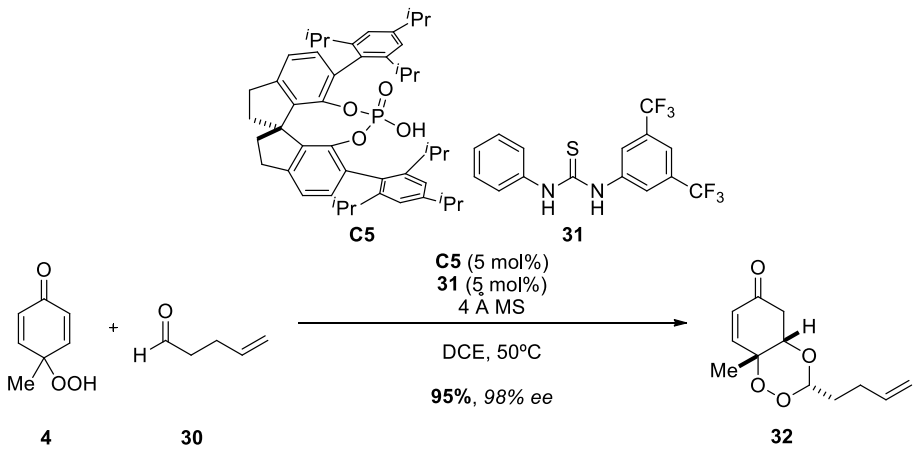
As an example of the enantioselective oxa- and aza-Michael reaction, bicycles **25**, **27** and **29** were obtained from the asymmetric cyclization of cyclohexadienones **24**, **26** and **28** (obtained under the oxidation conditions described in **Scheme 2.18**) in good yields, excellent diastereoselectivities (in terms of *cis*-fusion of the new generated cycle) and poor to moderate enatiomeric excess using the phosphoric acids derived from BINOL **C3** and **C4** as the catalyst of the conjugate addition (**Scheme 2.19**).



Scheme 2.19

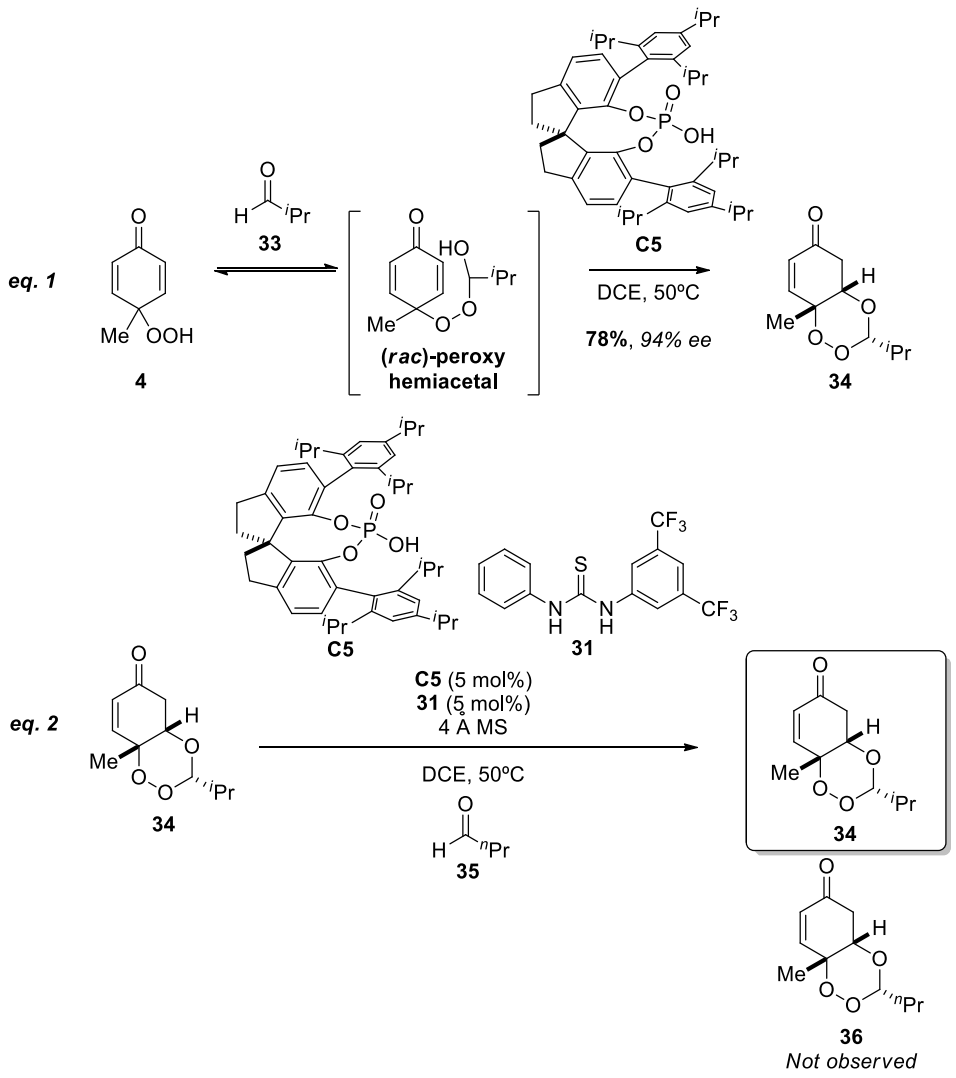
Rovis and co-workers also reported a desymmetrization oxa-Michael reaction from peroxyquinol **4** and aldehyde **30** in the presence of an enantiopure spirobiindane phosphoric acid derivative **C5** and the thiourea **31** (**Scheme 2.20**).[45] Trioxane derivatives **32** were obtained with high enantioselectivity when differently substituted aliphatic and aromatic aldehydes as well as different *p*-peroxyquinols were used. In all cases, the products were formed as a single diastereomer corresponding to the cis-fusion of the bicycle and the *trans* disposition of the substituent from the aldehyde and the the alkyl substituent at C-4 of the *p*-peroxyquinol. Achiral thiourea **31** was acting as an effective co-catalyst at low loadings of the chiral phosphoric acid, but was an ineffective catalyst by itself.

[45] Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554.



Scheme 2.20

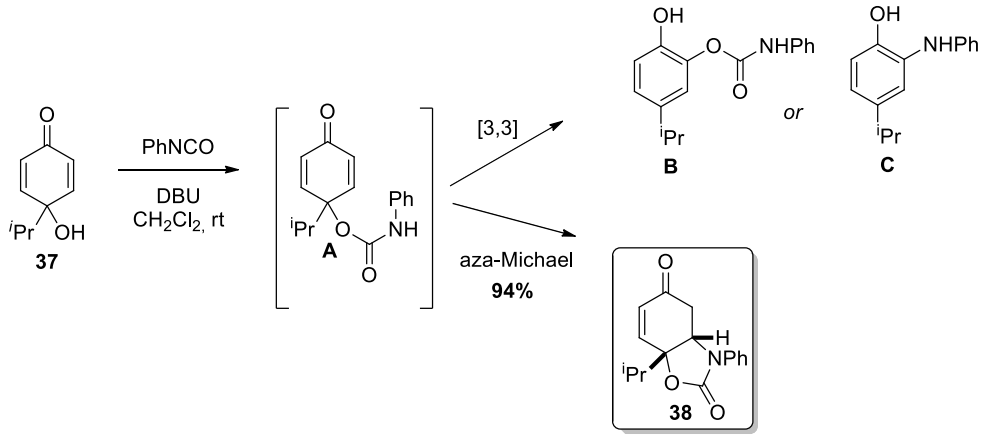
The authors explain that the enantiodetermining step is the oxa-Michael process and they propose a dynamic kinetic resolution of the racemic peroxy hemiacetal. The mechanism of this transformation is supported by the following experiment. Initially, *p*-peroxyhemiacetal is formed by heating *p*-peroxyquinol **4** with isobutyraldehyde **33**. Catalyst **C5** was then added to convert the intermediate *p*-peroxyhemiacetal into trioxane **34**. Under these conditions, a 78% yield of **34** was isolated as a single diastereomer with high enantiomeric ratio (**Scheme 2.21**, **eq. 1**). It was additionally confirmed when monitoring the reaction by HPLC throughout the course of the reaction the *p*-peroxyhemiacetal remained as racemate. A crossover experiment involving the reaction of **34** and *n*-butyraldehyde **35** revealed that the oxa-Michael step is not reversible under the reaction conditions and trioxane **36** is not observed (**Scheme 2.21, eq. 2**).



Scheme 2.21

In 2013, the stereoselective and chemoselective synthesis of bicyclic oxazolidinones from *p*-quinols and isocyanates was developed by the group of Zheng.[46] Reaction of differently substituted *p*-quinols such as **37** with different isocyanates such as phenyl isocyanate in the presence of DBU afforded the oxazolidinones **38** in good to excellent yields in a two-steps procedure. Although the carbamate intermediate **A** could undergo a [3,3]-sigmatropic rearrangement affording compounds **B** or **C**, the reaction was chemoselective since only the aza-Michael product **38** was observed. The reaction resulted in a totally diastereoselective process, and only the *cis*-fused diastereoisomer was obtained (**Scheme 2.22**).

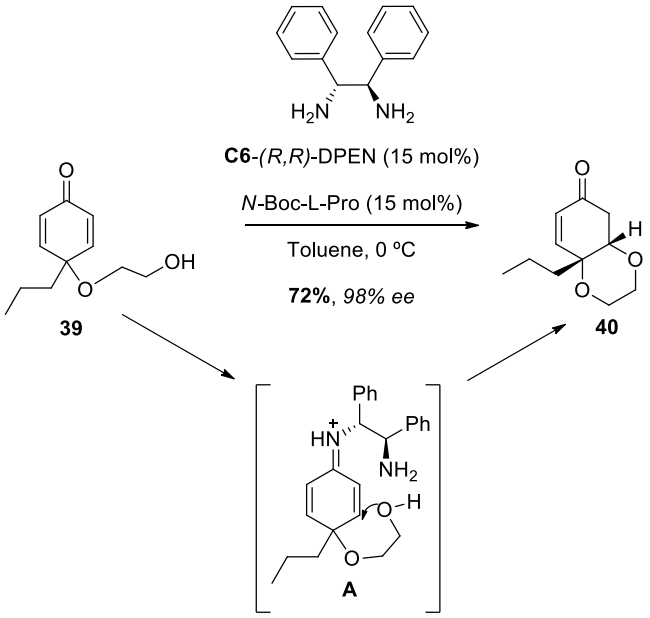
[46] Zhang, J.; Wu, J.; Yin, Z.; Zeng, H.; Khanna, K.; Hu, C.; Zheng, S. *Org. Biomol. Chem.* **2013**, *11*, 2939.



Scheme 2.22

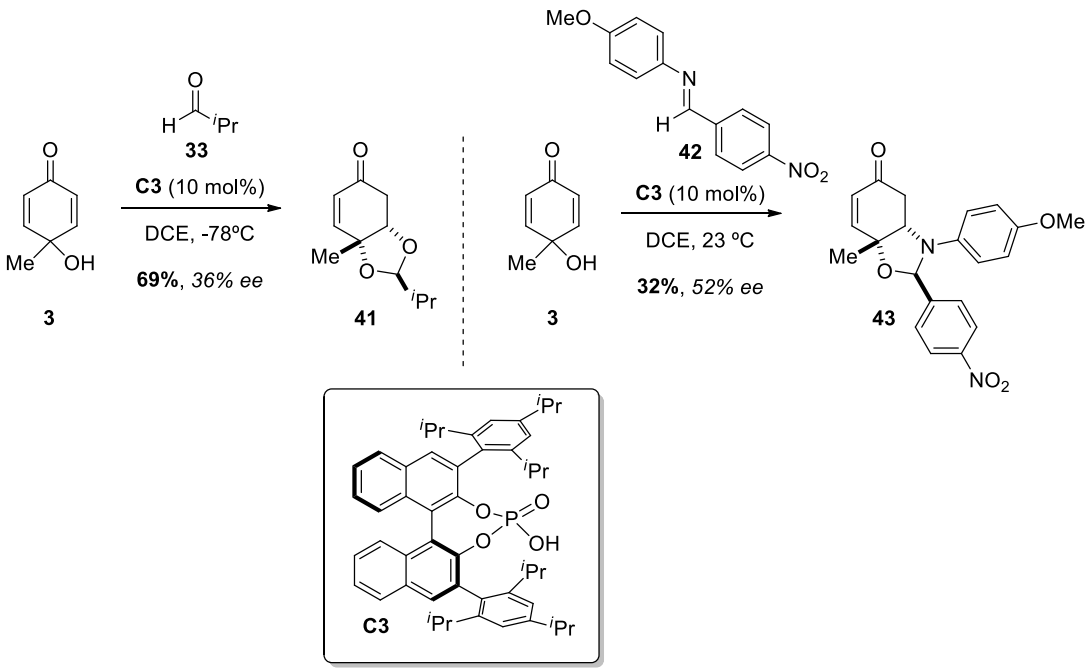
Ye and coworkers developed, in 2013, a primary-amine-salt catalyzed asymmetric intramolecular oxa-Michael reaction through iminium-based activation affording 1,4-dioxanes with excellent yields and enantioselectivities.[47] **C6**-(*R*,*R*)-1,2-diphenyl-ethyl-1,2-diamine (DPEN) mediated cyclization of cyclohexadienones derivatives such as **39** provided the iminium **intermediate A** which, after the oxa-Michael addition, afforded byclic dioxane derivatives **40** (**Scheme 2.23**). An amino acid such as *N*-Boc proline was required as an additive for the reaction to proceed. Substitution at the 4 position of the cyclohexadienone was well tolerated, as a variety of alkyl-, aryl-, and oxygen-substituted substrates cyclized efficiently. Increasing and decreasing the alcohol tether chain length resulted in the formation of nearly racemic products.

[47] Wu, W.; Li, X.; Huang, H.; Yuan, X.; Lu, J.; Zhu, K.; Ye, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1743.



Scheme 2.23

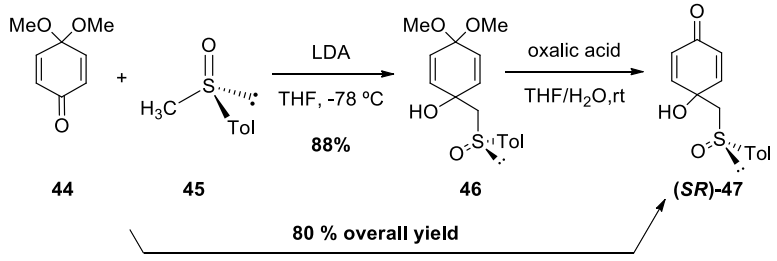
As mentioned before, during the development of the work corresponding to this Ph. D., the group of Rovis published, in 2014, the stereoselective synthesis of dioxolanes and oxazolidines via a desymmetrization acetalization/Michael cascade by reaction of *p*-quinols with aldehydes or imines in acidic media.[21b] They obtained good yields and diastereoselectivities by using the diphenylphosphinic acid (Ph_2PO_2H) as catalyst in the racemic synthesis of dioxolanes and oxazolidines from *p*-quinol **3**. They carried out only two examples of enantioselective desymmetrization (**Scheme 2.24**) obtaining moderate to good yields and poor to moderate enantiomeric excesses (35% yield, 36% *ee* for dioxolane **41** using aldehyde **33** and 53% yield, 52% *ee* for oxazolidine **43** using imine **42** as starting material).



Scheme 2.24

2.1.3. Precedents in our research group.

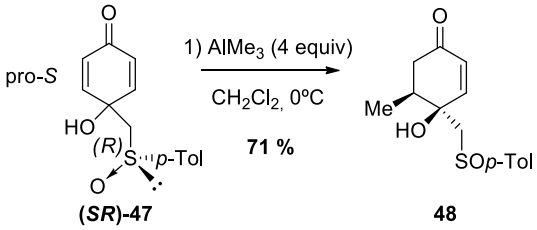
The synthesis and applications of *p*-quinols has been a subject of research in our group at the Universidad Autónoma de Madrid during the last decades. Initially, the synthesis of (*SR*)-4-hydroxy-4-(*p*-tolylsulfinyl)methyl-2,5-cyclohexadienone **47** was efficiently achieved by addition of the lithium anion derived from (*SR*)-methyl *p*-tolylsulfoxide **45** to *p*-benzoquinone dimethyl ketal **44**, followed by hydrolysis of the acetal group in **46**, in a 80 % overall yield (**Scheme 2.25**).[48] Other substituted derivatives were similarly obtained.[23a-b, 49]



Scheme 2.25

[48] Carreño, M. C.; Pérez González, Fischer, J. *Tetrahedron Lett.* **1995**, *36*, 4893.
[49] Carreño, M. C.; Pérez González, M.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 9128.

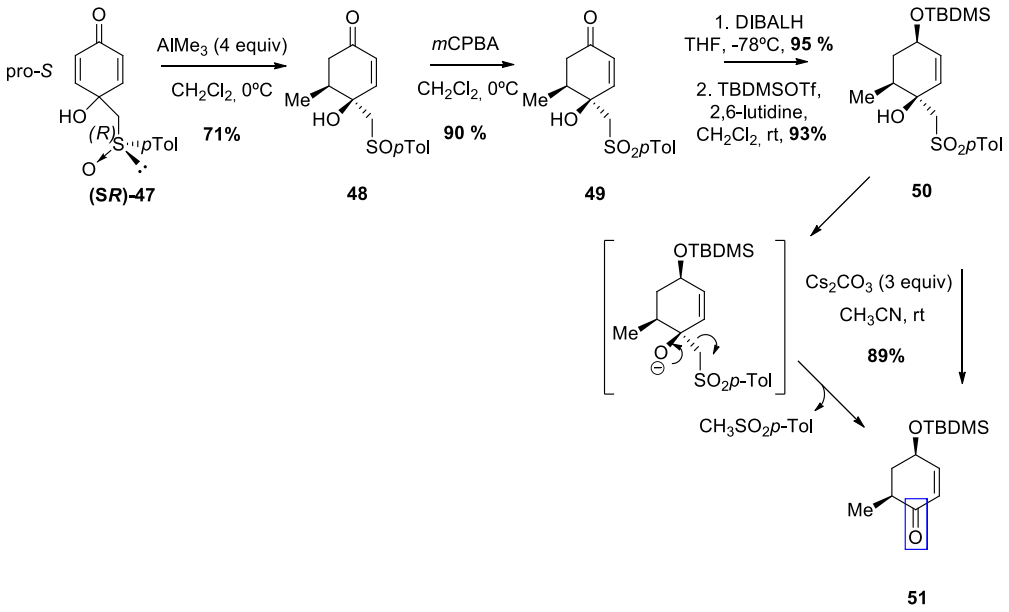
Stereoselective introduction of alkyl, vinyl, alkynyl[23a-b] or aryl[23c] groups in the conjugate positions of enantiopure (*SR*)-4-hydroxy-4-(p-tolylsulfinyl)methyl-2,5-cyclohexadienone **47** was efficiently developed by our research group (**Scheme 2.26**). In such *p*-quinol, the sulfoxide was able to direct the conjugate addition of trimethylaluminium leading to the exclusive formation of **48**. Only one, out of the four possible 1,4-addition diastereoisomers, was formed in the absence of any other metal catalyst in a highly chemo- and π-facial diastereoselective manner. The desymmetrization of the prochiral dienone moiety, reacting exclusively from the pro-*S* double bond *syn* to the face containing the OH at C-4, allowed the controlled formation of **48**.



Scheme 2.26

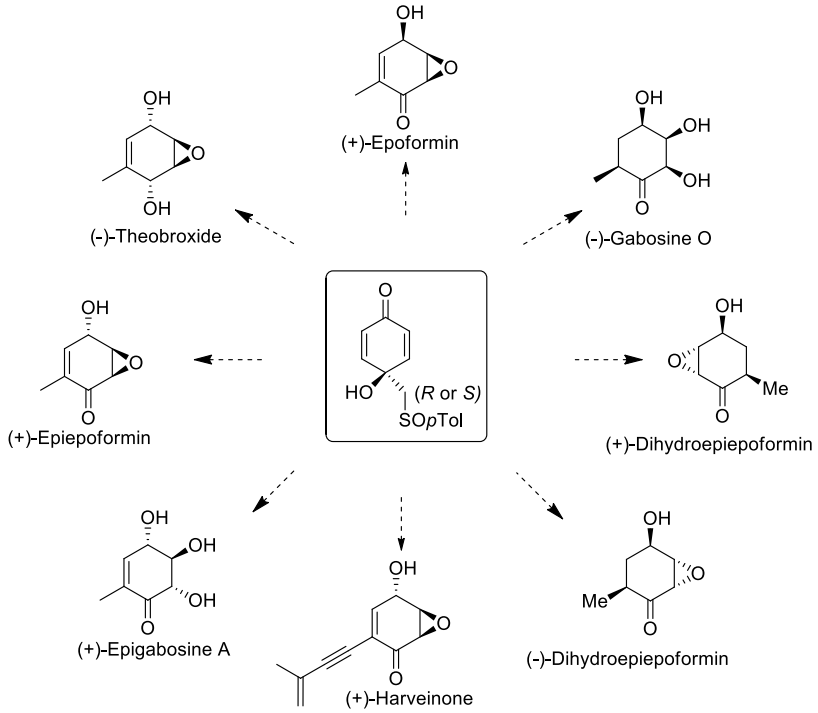
Looking for synthetic applications of this reaction, derivative **51** was synthetized following the synthesis depicted in **Scheme 2.27**. An other essential finding was that the γ-hydroxy sulfoxide situated on the cyclic system **48**, could be regarded as a chiral ketone equivalent, which can be recovered, after oxidation to sulfone (derivative **49**), under mild basic treatment through a retroaddition reaction of CH_3SO_2p-Tol affording derivative **51**.[50]

[50] Carreño, M. C.; Pérez-González, M.; Ribagorda, M.; Somoza, A.; Urbano, A. *Chem. Commun.* **2002**, 3052.



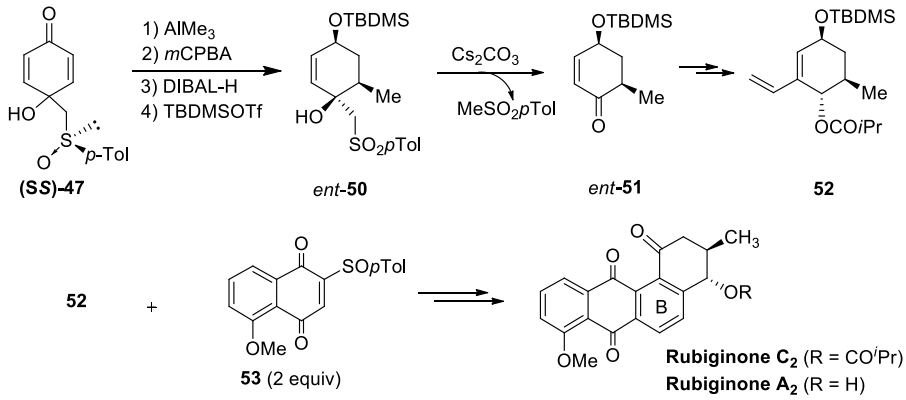
Scheme 2.27

Combining both findings, different natural polyoxigenated cyclohexane derivatives of huge interest due to their presence in different natural products, could be prepared. Some of the natural products synthetized using the stereoselective transformation of 4-hydroxy-4-[*p*-(tolylsulfinyl)methyl]-2,5-cyclohexadienone **47**, are shown in **Scheme 2.28**. Key steps were the stereo- and chemoselective conjugated addition of trialkyl or alkinyl aluminium derivatives to quinol **47**, followed by the elimination of the β-hydroxysulfinyl group situated at C-4, once the ring had been functionalized and the sulfoxyde group had been previously oxidized to the sulfone in order to recover a carbonyl group.[27a, 27c, 50]



Scheme 2.28

The enantio- and regioselective synthesis of angucyclinone-type antibiotics rubiginones A_2 and C_2[27b,51] (**Scheme 2.29**) was also achieved using a convergent strategy based on the Diels–Alder reaction between enantiopure (3S,5R,6S)-3,6-dihydroxy-5-methyl-1-vinylcyclohexene **52** and 2-*p*-tolylsulfinyl methyl juglone **53**. The diene partner could be synthesized from (SS)-**47** in nine steps with 26% overall yield, as depicted in **Scheme 2.29**.

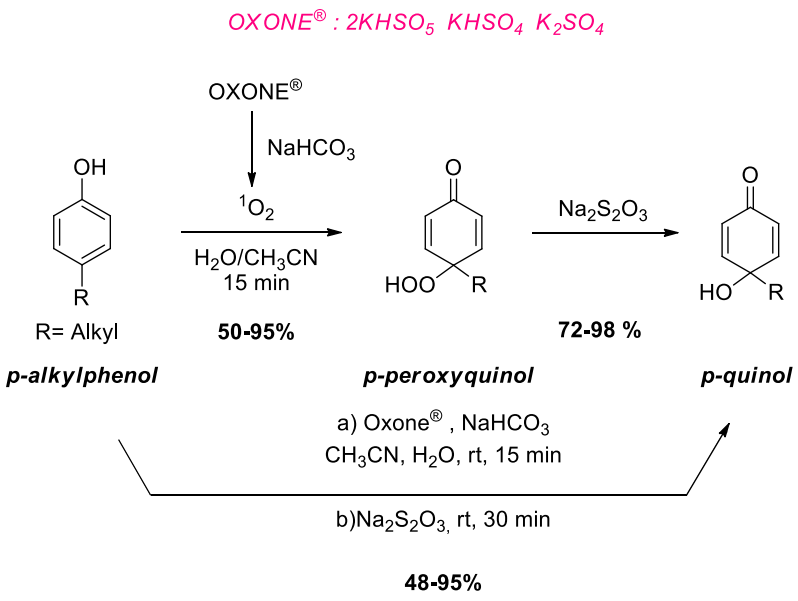


Scheme 2.29

[51] Carreño, M. C.; Ribagorda, M.; Somoza, A.; Urbano, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2755.

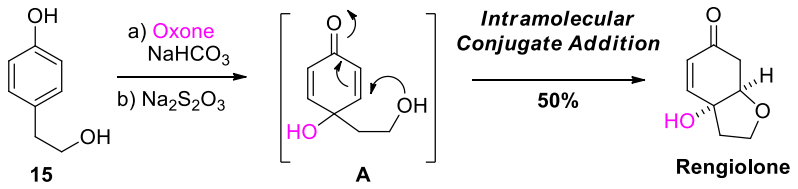
Thus, starting from sulfinyl *p*-quinol **(*SS*)-47**, cyclohexenone *ent*-**50** was obtained after $AlMe_3$ addition, oxidation of the sulfoxide, stereoselective DIBAL-H reduction of the carbonyl and TBDMS protection of the resulting OH. Treatment of sulfone *ent*-**50** with Cs_2CO_3, afforded the key enone *ent*-**51**, further transformed into the diene **52** in enantiopure form. The tetracyclic skeleton of Rubiginone was constructed in the reaction between enantiopure diene **52** and racemic 2-(*p*-tolylsulfinyl)-substituted juglone **53**, after a domino cycloaddition/sulfoxide elimination sequence, followed by an irradiation process which triggered another domino sequence including aromatization of B ring, TBDMS deprotection and oxidation at C-1, to afford Rubiginone C_2 later transformed into Rubiginone A_2 after the methanolysis of the pivaloate ester. The sulfoxide played a double role in this reaction, controlling the regioselectivity of the Diels-Alder process and facilitating the recovery of the quinone structure after the cycloaddition. The total enantioselective synthesis was thus achieved in only 11 and 12 steps from *p*-quinol **(*SS*)-47** with >98% *ee* and 4.4 and 4.8% overall yield, for rubiginones C_2 and A_2.

More recently, a new procedure to synthesize *p*-quinols using Oxone® as a source of singlet oxygen, has been applied.[36] The production of singlet oxygen ($^1O_2$) from a mixture Oxone®/$NaHCO_3$ had been reported in 1956,[38] but its use in synthesis of *p*-quinols from *p*-alkylphenols had not been investigated up to 2006. The procedure implies treatment of a *p*-alkylphenol with Oxone®, an inexpensive and easily handled solid consisting of a 2:1:1 mixture of $KOSO_2OOH$, $KHSO_4$, and K_2SO_4, and a saturated solution of $NaHCO_3$. After reduction of the initially formed hydroperoxides which could be isolated, *p*-quinols were formed in good to excellent yields (**Scheme 2.30**).



Scheme 2.30

This method was applied in this group as a key step in the synthesis of different *p*-quinols en route to interesting products. Thus, the stereocontrolled synthesis of polyoxygenated hydrobenzofurans and hydrobenzopyrans from adequately substituted *p*-peroxy quinols or *p*-quinols have been described by our research group.[52] In the example shown in **Scheme 2.31**, the synthesis of Rengiolone, was directly achieved from *p*-(2-hydroxyethyl)phenol **15** by oxidative dearomatization with Oxone® followed by reduction with $Na_2S_2O_3$. The *p*-quinol **intermediate A** formed under these conditions spontaneously evolved through an oxa-Michael addition giving the natural product.[52]

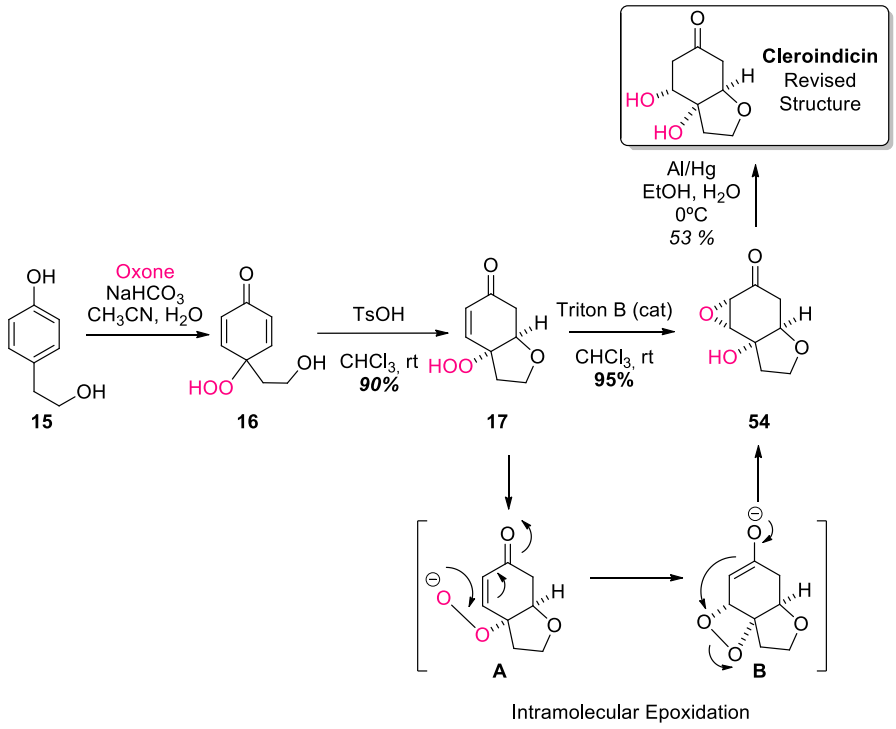


Scheme 2.31

An acidic-basic tandem catalytic process on the intermediate *p*-peroxy quinol formed from *p*-alkyl phenols, adequately substituted at C-4 with hydroxyl alkyl chains, allowed the one-pot synthesis of natural Cleroindicin D in excellent yields and diastereoselectivities

[52] Barradas, S.; Carreño, M. C.; González-López, M.; Latorre, A.; Urbano, A. *Org. Lett.* **2007**, *9*, 5019.

(**Scheme 2.32**). Thus, after adding Oxone® to the *p*-alkyl phenol **15**, the intermediate hydroperoxide **16** was treated with *p*-TsOH. The acid was promoting the fast and diastereoselective intramolecular conjugate addition of the primary OH, affording in 90% yield hydrobenzofuran **17**, still bearing an enone fragment and the hydroperoxide group. Upon treatment with 0.12 equiv of Triton-B in $CHCl_3$, bicyclic hydroperoxide **17** provided tricyclic epoxide **54** as the unique diastereomer in an excellent 95% yield. The formation of the epoxide took place exclusively on the same face of the cyclohexenone bearing the OOH group of derivative **17** probably through the evolution of a dioxetane intermediate such as **B** formed after intramolecular conjugate addition of the hydroperoxide anion to the cyclohexenone moiety, under the basic conditions (**A**). The first total synthesis of natural **Cleroindicin D** was thus achieved in three steps and 36% overall yield from a commercially available phenol (**Scheme 2.32**). This synthesis allowed the structural revision of the natural product which had not been correctly established.

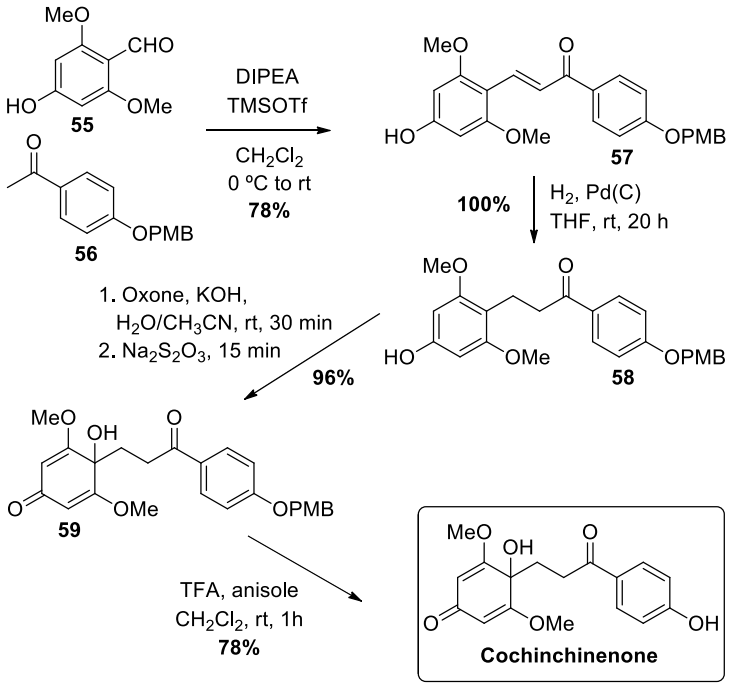


Scheme 2.32

Cochinchinenone, a novel chalcone constituent having a *p*-quinol moiety in ring A of its structure, was isolated in 2007 from the stems of *Dracaena cochinchinensis* and showed growth inhibitory effects against *Helicobacter pylori* (ATCC43504).[14] Our research group

developed a total synthesis[15] based on this methodology for the synthesis of *p*-quinols from *p*-alkylphenols previously reported by this group.

The synthesis of **Cochinchinenone** was achieved as shown in **Scheme 2.33**. Thus, a Mukaiyama aldol reaction mediated by TMSOTf between aldehyde **55** and OPMB-protected acetophenone **56** allowed the synthesis of chalcone **57** having the carbon skeleton found in the natural product. Reduction of the double bond gave rise to the OPMB-protected *bis*-phenol **58** in quantitative yield. The oxidative dearomatization of **58** (Oxone®, KOH, H_2O/CH_3CN, rt, 30 min) followed by in situ $Na_2S_2O_3$ reduction of the initially formed *p*-peroxyquinol, afforded the corresponding OPMB-protected *p*-quinol **59**, in an excellent 96% yield. The last step of the synthesis of Cochinchinenone, the treatment of OPMB-protected compound **59** with trifluoroacetic acid (TFA) in the presence of anisole,[53] afforded Cochinchinenone, identical to the natural product.



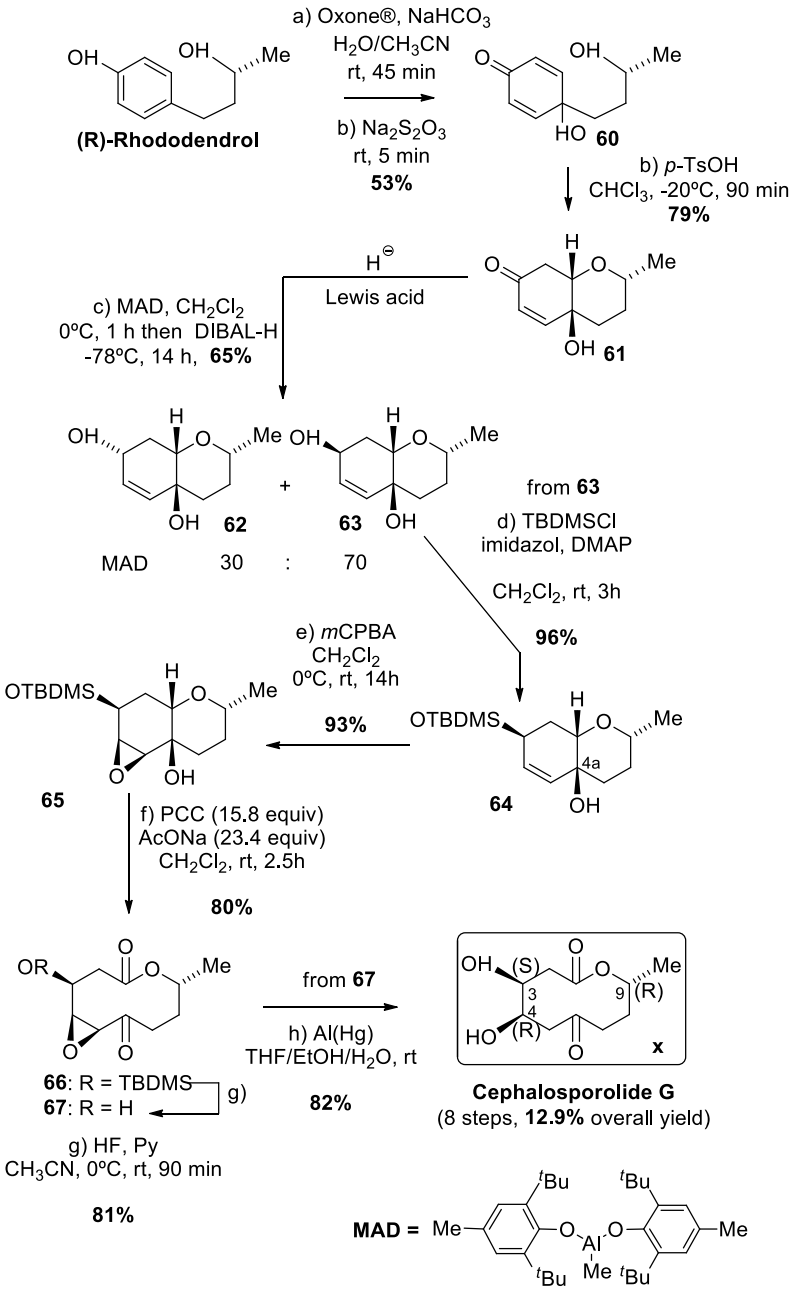
Scheme 2.33

Following this methodology the synthesis of Chepalosporolide G,[54] a member of the natural 10-membered lactone family, was also achieved (**Scheme 2.34**). Thus, starting from (*R*)-Rhododendrol, treatment with Oxone® in the presence of $NaHCO_3$, followed by the in situ

[53] (a) Yan, L.; Kahne, D. *Synlett*, **1995**, 523. (b) Stallforth, P.; Adibekian, A.; Seeberger, P. H. *Org. Lett*. **2008**, *10*, 1573.
[54] Barradas, S.; Urbano, A.; Carreño, M. C. *Chem. Eur. J.* **2009**, *15*, 9286.

addition of $Na_2S_2O_3$, afforded *p*-quinol (*R*)-**60**. A stereoselective (95:5 *dr*) conjugate addition of the primary OH of the hydroxybutyl chain at C_4 to one of the double bonds of **60**, promoted by a catalytic amount of *p*-TsOH afforded **61** In this step, the efficient differentiation of the two diastereotopic faces and the two diastereotopic double bonds of the cyclohexadienone moiety of *p*-quinol **60** was achieved. Stereoselective reduction of compound **61** with DIBAL-H in the presence of the bulky Lewis acidic reagent methyl aluminum *bis*-(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD),[55] gave a 30:70 mixture of alcohols **62** and **63**, from which the desired diastereoisomer **63** was isolated pure in 65% yield, after chromatographic separation. After protection of the secondary alcohol of compound **63** as OTBDMS **64**, treatment with *m*CPBA afforded tricyclic compound **65**, as the only diastereomer, by exclusive upper face epoxidation of the double bond of **64**. Treatment of this tricyclic epoxide **65** with PCC in the presence of NaOAc gave rise, to the 6-keto ten-membered lactone **66**, after an efficient oxidative cleavage-ring expansion process. Deprotection of the OTBDMS followed by regioselective reductive opening of the epoxide of **67** afforded **Chephalosporolide G** thus synthesized, for the first time, in only 8 steps and 12.9% overall yield starting from natural phenol (*R*)-Rhododendrol.

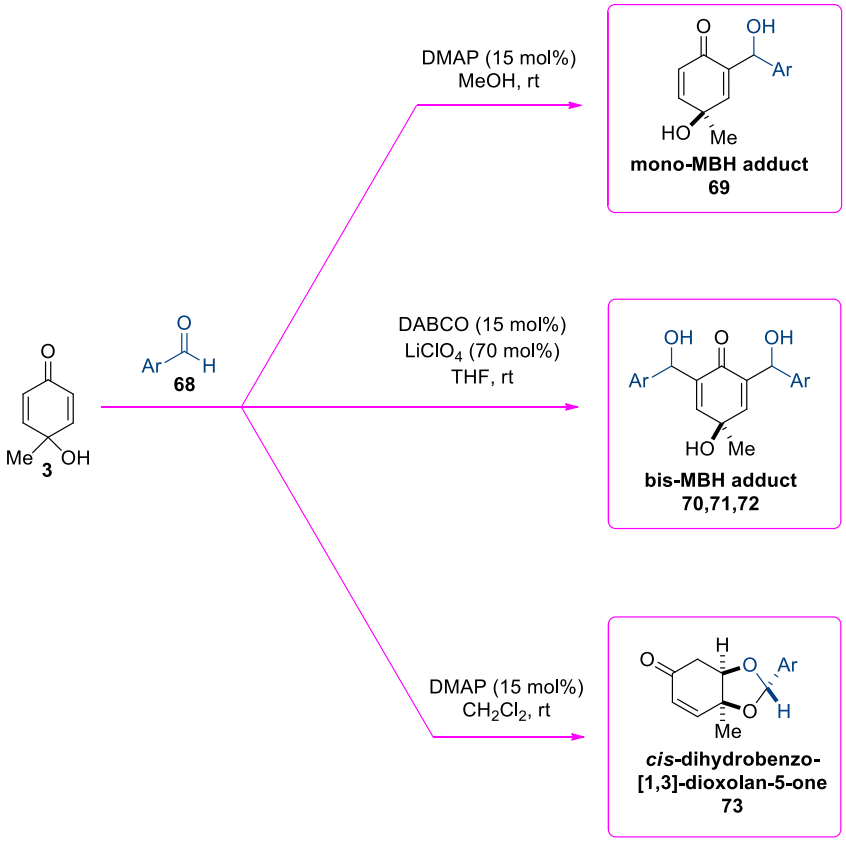
[55] a) Ooi, T.; Maruoka, K. *Rev. Heteroatom Chem.* **1998**, *18*, 61; b) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650.



Scheme 2.34

As mentioned in Chapter 1, the inmediate precedent of the work developed in this Ph D Thesis corresponds to a preliminary study of the Morita-Baylis-Hillman reaction[18] between 4-methyl-4-hydroxy-2,5-cyclohexadienone **3** and aromatic aldehydes **68**.[19] This study revealed again a singular behavior of *p*-quinols as ambident systems. The structures of the final products were shown to be dependent on reaction conditions. Under basic catalytic conditions, not only the base chosen was defining the product, the choice of solvent was also critical. Thus, using DMAP (dimethyl aminopyridine) in MeOH mono-MBH adducts **69** resulted. The combination DABCO (1,4-diazabicyclo[2.2.2]octane)/$LiClO_4$ gave the bis adducts **70-72**. Changing the solvent in the DMAP catalyzed process, in CH_2Cl_2, afforded the *cis*-dihydrobenzo-

[1,3]-dioxolan-5-one structures **73** as the result of an acetalization/oxa-Michael addition domino process (**Scheme 2.35**).



Scheme 2.35

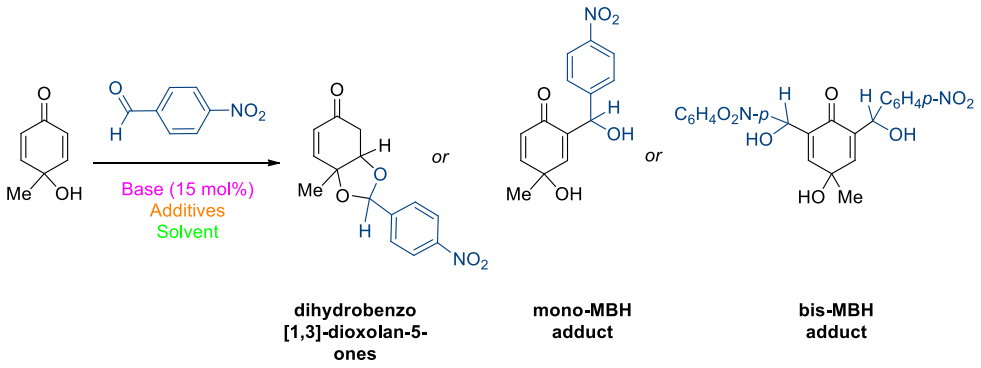
OBJECTIVES

Taking into account all the work previously reported in the literature as well as our expertise in the synthesis and study of *p*-quinols, we considered the following objective for the second Chapter of this Ph D work:

Study of base catalyzed reactions of *p*-quinols with aldehydes and imines

In spite of the huge synthetic potential of the *p*-quinol derivatives, a base catalyzed acetalization/oxa-Michael domino process had never been explored before, and only the preliminary results previously indicated had been published.

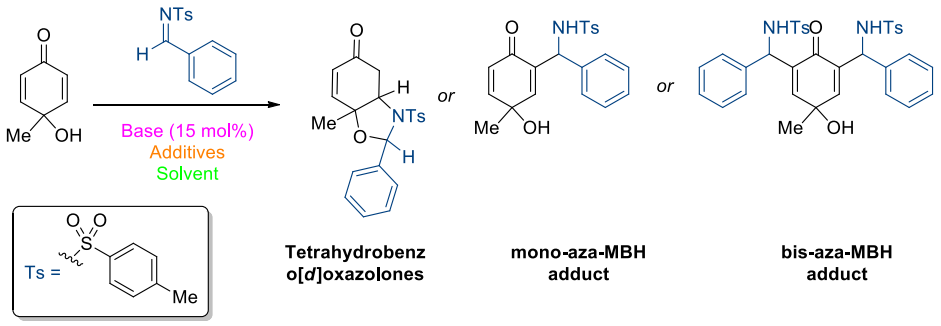
We decided to complete the initial study in order to determine the scope of the base catalyzed reactions between the *p*-quinols and aldehydes. The variation of the catalytic base as well as the solvent or the presence of additives will be considered on the model reaction shown in **Scheme 2.36** between 4-methyl-4-hydroxy-quinol and *p*-nitrobenzalhehyde, choosen as a reactive aldehyde in order to obtain selectively the acetalization/oxa-Michael product or MBH-adducts.



Scheme 2.36

Later, other aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldehydes will be tested in order to evaluate the influence of electron withdrawing or electron donating substituents in the synthesis of dihydrobenzo[*d*][1,3]-dioxol-5(7aH)-ones.

Finally, the unprecedented base catalyzed reaction of *p*-quinols with different imines and ketimines will be studied (**Scheme 2.37**).



Scheme 2.37

Different nucleophilic bases as well as solvents will be tested in the model reaction between 4-methyl-4-hydroxy-2,5-cyclohexadienone and *N*-tosylbenzaldimine shown in **Scheme 2.37**. The influence of substitution on the aromatic rings of both the sulfonylamide fragment and the aromatic aldehyde precursor of the imine, will be studied in order to know the efficiency of the process to obtain the Aza-MBH adducts and/or a *N*,*O*-aminal derivatives.

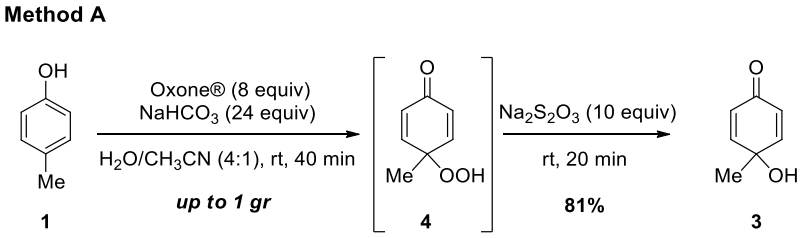
Aromatic, α,β-unsaturated, aliphatic aldimines, sulfonyl ketimines and differently *N*-protected benzaldimines differently substituted will be tested.

2.2. Results.

2.2.1. Synthesis of starting materials.

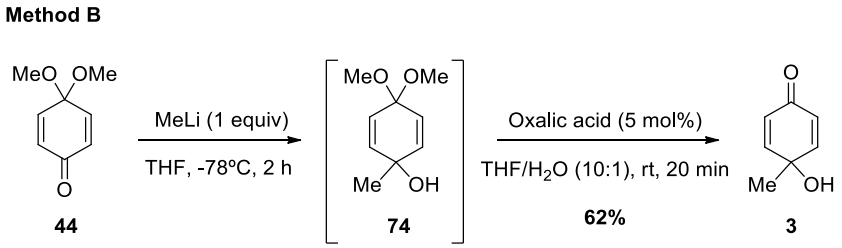
Synthesis of p-quinols.

The symmetrically substitued *p*-quinol **3** was prepared following different procedures, depending on the relative amount required. For a 8 mmol (1 g) scale **Method A** (**Scheme 2.38**) was employed using *p*-cresol **1** as the commercially available starting material. This methodology is based on the one-pot/two steps oxidative dearomatization process of *p*-alkylphenols with Oxone®/$NaHCO_3$ as source of singlet oxygen ($^1O_2$), followed by in situ reduction of the *p*-peroxyquinol intermediate **4** with $Na_2S_2O_3$, developed by our research group.[36] The dearomatization reaction of *p*-cresol occured by treatment of a solution of **1** in a 4:1 mixture of H_2O/CH_3CN, with 8 equivalents of Oxone® and 24 equivalents of $NaHCO_3$ at room temperature. Once the oxidation of *p*-cresol was completed (40 min) leading the *p*-peroxyquinol **4**, the addition in situ of 10 equivalents of $Na_2S_2O_3$ over the crude mixture gave *p*-quinol **3** which was isolated in 81% yield, after flash column chromatography (**Scheme 2.38**).



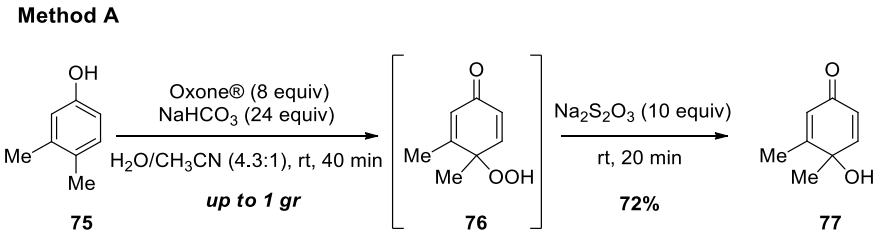
Scheme 2.38

Application of this method to the synthesis of higher amounts required great volumes of $NaHCO_3$ solution which made the isolation difficult, thus decreasing the yield significantly. We scaled up the synthesis of **3** (up to 40 mmol, 5 g) using a different strategy based on the addition of 1 equivalent of MeLi to a THF solution of the *p*-benzoquinone dimethyl monoketal **44**[28a] at -78°C (**Scheme 2.39**). After two hours the crude reaction afforded *p*-quinol dimethylketal **74**. Hydrolisis of the resulting monoketal **74** with 5 mol% of oxalic acid in a 10:1 mixture of THF/ H_2O at room temperature led to the *p*-quinol **3** which was isolated pure in 62% yield (**Scheme 2.39**).



Scheme 2.39

The synthesis of 3-methyl substituted *p*-quinol **77** was achieved following the previously described **Method A** for the oxidative dearomatization of *p*-alkylphenols using Oxone®/$NaHCO_3$ as the source of singlet oxygen and $Na_2S_2O_3$ as the reducting agent of the non-isolated *p*-peroxyquinol intermediate **76**. *p*-Quinol **77** was thus obtained in a 72% isolated yield from *p*-alkylphenol **75** using the same relative amounts of Oxone®, $NaHCO_3$ and $Na_2S_2O_3$ but in a 4.3:1 mixture of H_2O/CH_3CN (**Scheme 2.40**).



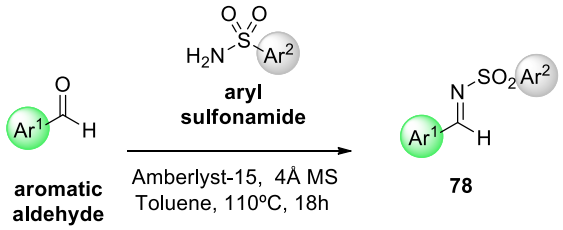
Scheme 2.40

Synthesis of sulfonyl benzaldimines.

To study the reactions of *p*-quinols with benzaldimines, the choice of the nitrogen protecting group was essential to avoid decomposition. The aryl sulfonamide protection was chosen due to its robustness.

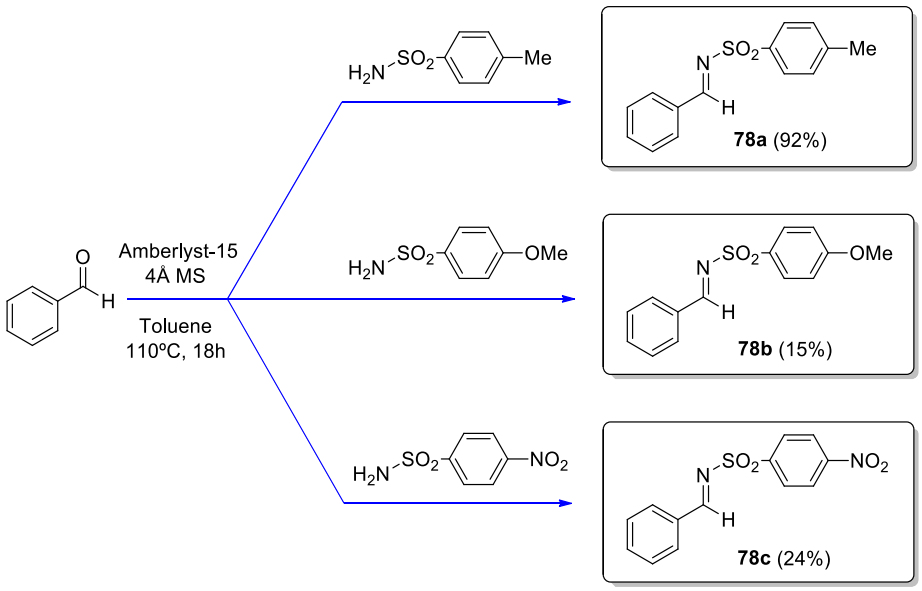
The synthesis of sulfonyl benzaldimines **78** was achieved following the methodology described by Davis.[56] This method consists on the condensation of the corresponding aromatic aldehyde and the aryl sulfonamide using Amberlyst 15 as the acid catalyst, and activated 4Å MS to eliminate water from the medium (**Scheme 2.41**).

[56] Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1987**, *66*, 203.



Scheme 2.41

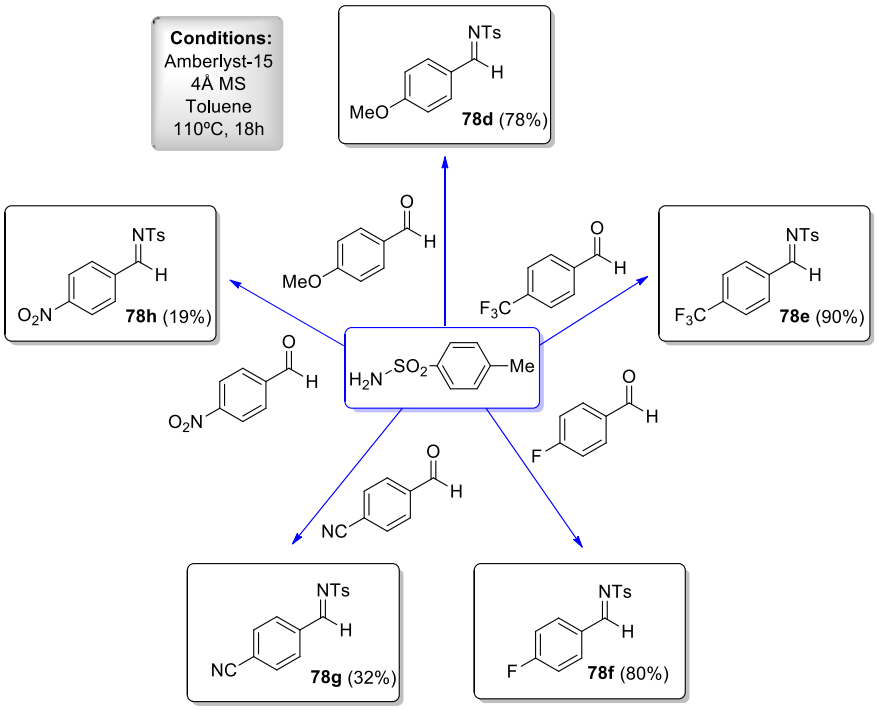
As previously mentioned, in order to study the influence of the electronic nature of the aromatic ring on the reactivity of aryl imines, we synthetized either imines with electron donor substituents in the *para* position of the sulfonyl aryl ring and imines with electron withdrawing substituents (Ar_2). Under the conditions described before, *p*-tolyl sulfonyl benzaldimine **78a** was obtained in 92% yield from the condensation of benzaldehyde and tosylamide. *p*-Methoxy sulfonyl benzaldimine **78b** was obtained, in only 15% yield, by reaction of benzaldehyde with *p*-methoxy phenyl sulfonamide. The reaction of benzaldehyde and *p*-nitrosulfonyl amide under the conditions previously reported, afforded *p*-nitrosulfonyl benzaldimine **78c** in 24% yield (**Scheme 2.42**).



Scheme 2.42

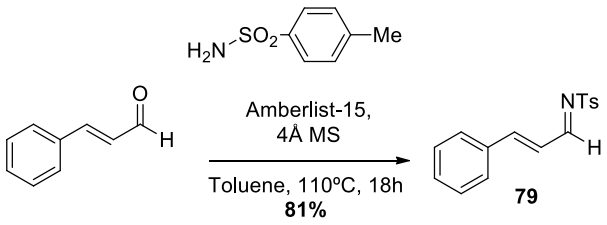
Then, the synthesis of different *p*-toluene sulfonyl (Ts: $\mathbf{Ar^2}$ = *p*-Me-C_6H_5) protected aryl aldimines with different substituents on the aromatic ring of the starting aldehyde ($\mathbf{Ar^1}$), was developed. Thus, an imine with an electron donor substituent in the *para* position of the aromatic aldehyde precursor was synthetized by reaction between anisaldehyde and *p*-toluene sulfonyl amide, in the presence of Amberlyst-15. As depicted in **Scheme 2.43** under the conditions shown, the aldimine **78d** was isolated in 78% yield. Imines with electron

withdrawing groups at the *para* position of the aromatic aldehyde were also synthetized. Thus, 80% yield of isolated tosyl-*p*-trifluoromethylbenzaldimine **78e** and 90% yield of pure tosyl-*p*-fluorobenzaldimine **78f**, were obtained using Amberlyst-15 as catalyst in refluxing toluene. The use of *p*-cyanobenzaldehyde or *p*-nitrobenzaldehyde did not afford as good results. Thus, *p*-cyanobenzaldehyde was condensed with tosylamide under the same experimental conditions as above, affording **78g** in 32% yield. Similar results were obtained in the case of the synthesis of tosylsulfonyl-*p*-nitrobenzaldimine **78h**, which was isolated in 19% yield. (**Scheme 2.43**).



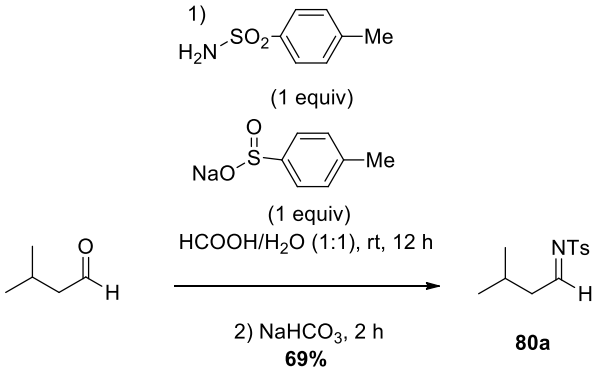
Scheme 2.43

Other sulfonyl imines were synthetized in order to study their reactivity. Thus, the phenyl-α,β-unsaturated tosyl imine **79** was obtained following the same procedure as previously described, by condensation of cinnamaldehyde with tosylamide obtaining 81% yield (**Scheme 2.44**).



Scheme 2.44

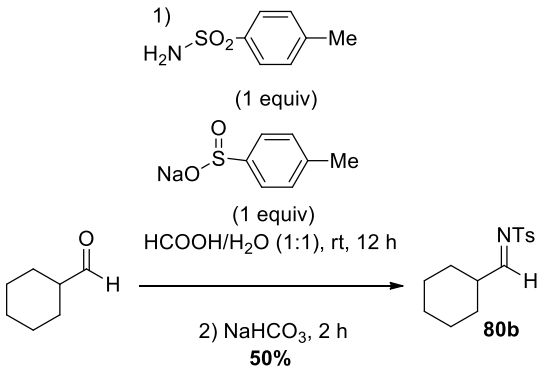
We later synthetized different aliphatic sulfonyl imines in order to check their behavior in the reaction with *p*-quinols. Thus, 4-methyl-*N*-(3-methylbutylidene)benzenesulfonamide **80a** was synthetized following the procedure described by the group of Normant[57] based on the reaction of an aliphatic aldehyde with *p*-toluenesulfonylamide and sodium *p*-tolylsulfinate in a formic acid solution. After stirring the mixture 12 hours, a solution of $NaHCO_3$ was added. The 4-methyl-*N*-(3-methylbutylidene)benzenesulfonamide **80a** was isolated in 69% yield (**Scheme 2.45**).



Scheme 2.45

Using the same methodology, *p*-toluenesulfonylcyclohexyl aldimine **80b** was synthetized by the reaction of cyclohexanecarboxaldehyde with *p*-toluenesulfonylamide and sodium *p*-tolylsulfinate, in a formic acid solution. After stirring the mixture 12 hours, a solution of $NaHCO_3$ was added. Tosyl aldimine **80b** was isolated in 50% yield (**Scheme 2.46**).

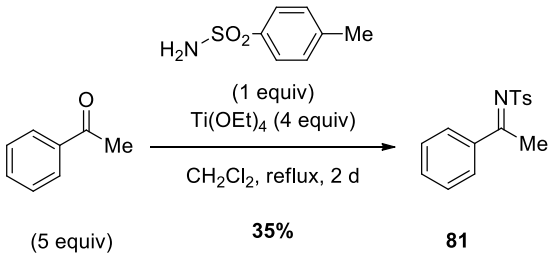
[57] Chemla, F; Hebbe, V.; Normant, J-F. *Synthesis* **2000**, *1*, 75.



Scheme 2.46

Synthesis of other imines.

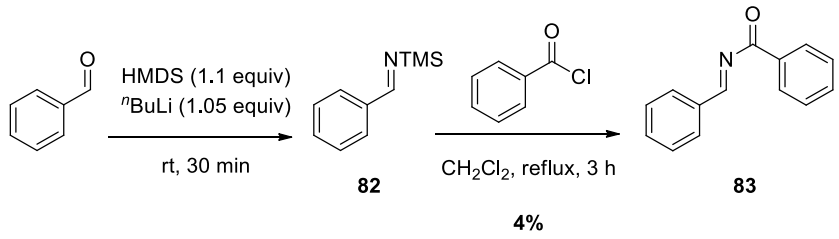
To study the reactivity of sulfonyl ketimines with *p*-quinols, ketimine **81** was synthetized following the methodology previously described in the literature[58] based on the condensation of 5 equivalents of acetophenone with *p*-toluenesulfonylamide in the presence of 4 equivalents of titanium tetraethoxide in refluxing CH_2Cl_2. After for 2 days, a 35% yield of pure phenylmethyltosylketimine **81** was obtained (**Scheme 2.47**).



Scheme 2.47

Although the sulfonamides were the main substrates studied, *N*-benzoyl benzaldimine was also synthetized in order to evaluate the influence of a different protecting group on the imine in the final results of its base catalyzed reaction with *p*-quinols. Thus, we synthetized the benzamide **83** following the procedure described in the literature,[59] in which the trimethyl silyl imine **82** was firstly obtained from benzaldehyde and lithium hexamethyldisilazide (LHMDS) and treated with benzoyl chloride. Although the yield reported was 98%, we only could isolate the benzoyl imine in only a 4% yield (**Scheme 2.48**).

[58] Kwak, S. H.; Lee, S. A.; Lee, K.-I. *Tetrahedron: Asymmetry* **2010**, *21*, 800.
[59] Lou, S.; Moquist, Philip, N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.



Scheme 2.48

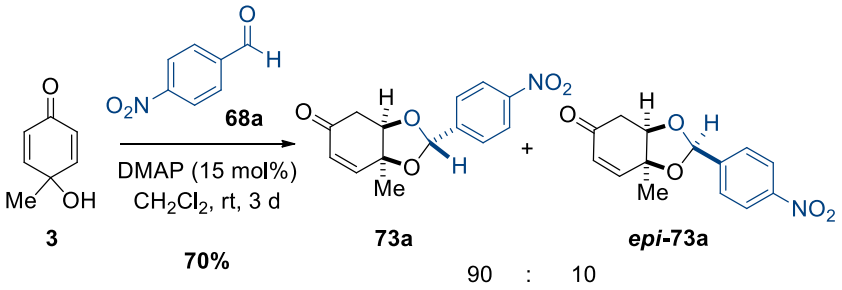
2.2.2. Study of base catalyzed reactions of p-quinols with aldehydes.

Reactions of p-quinols with aromatic aldehydes.

As it has been previously mentioned, the first objective of this chapter consisted on the study of reactions of *p*-quinols with aldehydes using basic catalysis.

The direct precedent of this work corresponds to the study published in 2010 by our research group where the behavior of *p*-methylquinols under Morita-Baylis-Hillman reaction conditions with aromatic aldehydes was explored.[19]

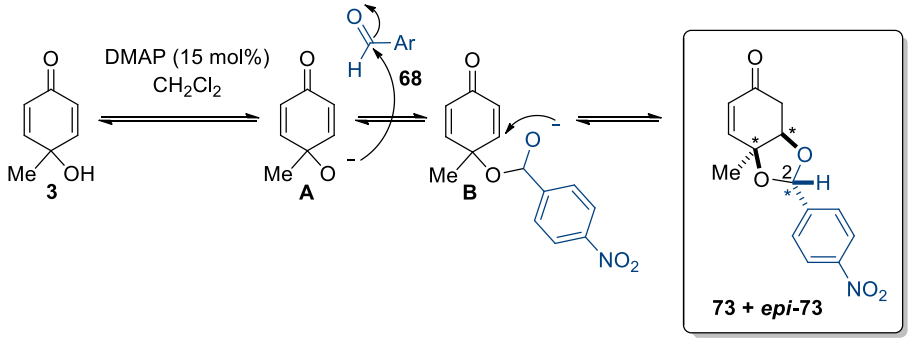
This previous investigation evidenced the importance of solvent and additives on the final results. As a model example, the reaction shown in **Scheme 2.49**, between *p*-methyl quinol **3** and *p*-nitrobenzaldehyde **68a** in the presence of DMAP (dimethyl aminopyridine) and CH_2Cl_2, led to a 90:10 mixture of epimeric dioxolanes **73** and ***epi*-73** instead of the expected Morita-Baylis-Hillman adducts.



Scheme 2.49

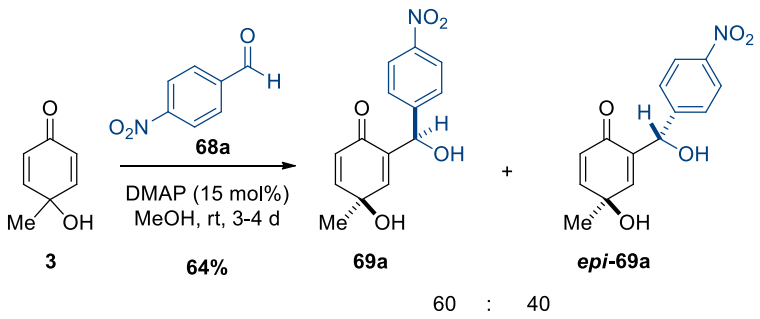
Similar results were obtained when DABCO (1,4-diazabicyclo[2.2.2]octane) was used as catalytic base in CH_2Cl_2, though the reaction was not completed. The formation of the cyclic

acetal presumably involved a base-promoted 1,2-addition of the hydroxyl group of the *p*-quinol **3**, acting as a nucleophile (**A**), to the carbonyl aldehyde, followed by an intramolecularoxa-Michael addition of the intermediate alkoxide **A** to the cyclohexadienone moiety (**B**) (**Scheme 2.50**).



Scheme 2.50

The use of a protic solvent such as MeOH, that is known to enhance the rate of MBH processes,[60] afforded the mono MBH-adducts **69a** and ***epi*-69a** in a 60:40 mixture of diastereomers that were separated by chromatography (**Scheme 2.51**).

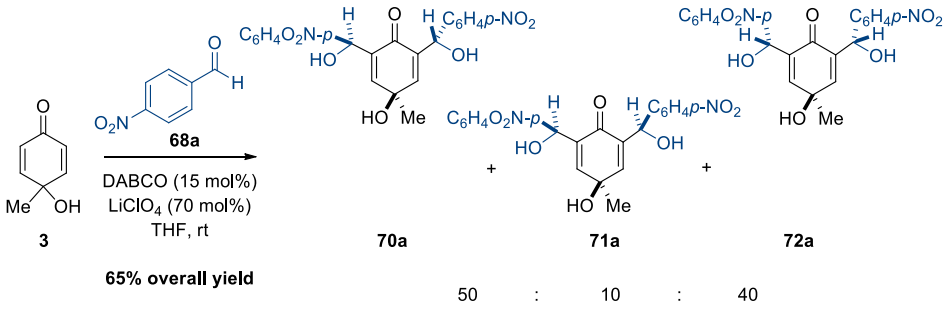


Scheme 2.51

Other nucleophilic bases such as DABCO gave similar results in the presence of protic solvents. When the reaction of *p*-quinol **3** and *p*-nitrobenzaldehyde **68a** was performed with

[60] (a) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513; (b) Park, K.-S.; Kim, J.; Choo, H.; Chong, Y. *Synlett.* **2007**, *3*, 395; (c) Cai, J.; Zhou, Z.; Tang, C. *Org. Lett.* **2002**, *4*, 4723; (d) Aggarwal, V. K.; Fean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510; (e) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369; (f) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *6*, 5413; (g) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165; (h) Auge, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* **1994**, *35*, 7947; (i) Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1998**, *18*, 495.

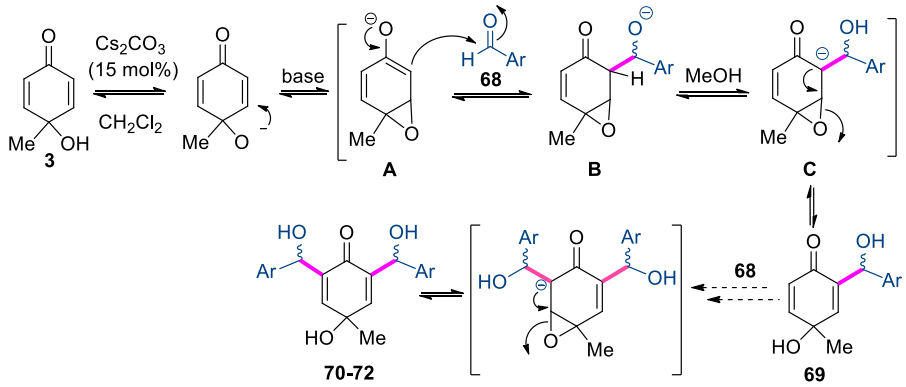
DABCO (15 mol%) and a co-catalyst such as $LiClO_4$ (70 mol%)[61] in THF, the double MBH-adducts were formed as a 50:10:40 mixture of diastereoisomers **70a**, **71a** and **72a** in 65% total yield (**Scheme 2.52**).



Scheme 2.52

An important finding of this previous study was that these MBH reactions only occurred if the OH of the *p*-quinol was free (the OMe derivative did not react under the same conditions). As previously reported by our research group,[19] the reaction could be also promoted by a non-nucleophilic base such as Cs_2CO_3 in MeOH, thus suggesting that the deprotonation of the *p*-quinol OH was the initial step in the mechanism (**Scheme 2.53**). Once the acid-base equilibrium generates the alkoxide anion of *p*-quinol, an entropically favored oxa-Michael intramolecular addition produced the enolate expoxide intermediate **A**. Subsequent aldol reaction with **68** (**B**) and abstraction of the acidic α-proton, favored by the protic solvent, could explain the formation of a new enolate-epoxide **C**, which evolves into the Baylis-Hillman adduct **69** by epoxide ring opening. The double-MBH adducts (**70-72**) could be formed through an analogous sequence from other molecule of **68**.

[61] Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.



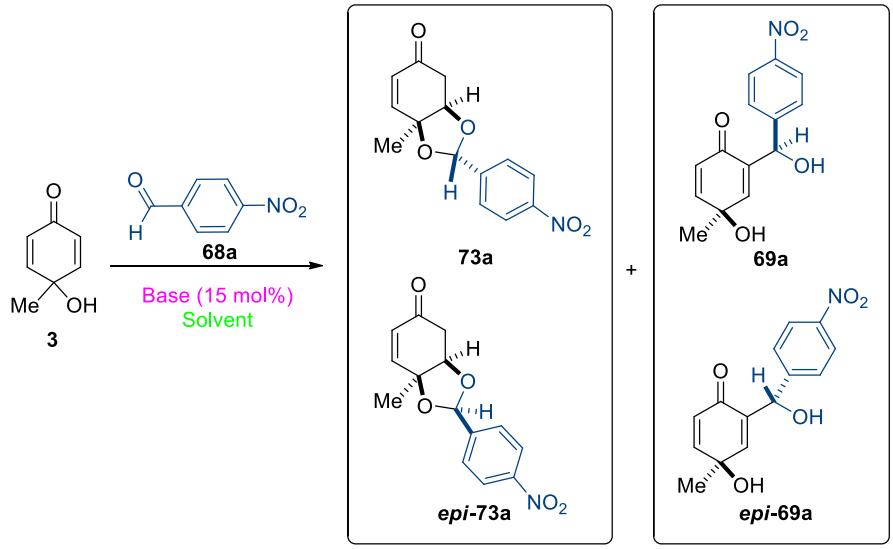
Scheme 2.53

All these results were of huge interest since this was the first study carried out on base catalyzed reactions of *p*-quinols with aldehydes.

To complete this study, the mentioned model reaction was further investigated in order to find the best conditions en route to the hydrobenzodioxolanones previously obtained. The *p*-nitrobenzaldehyde **68a** was choosen as a model due to its high electrophilic character, increased by the electron with-drawing nitro group.

The reaction of *p*-quinol **3** and *p*-nitrobenzaldehyde **68a** in the presence of DABCO as catalyst was carried out in two different solvents. As shown in **Table 2.1** (**entry 1**) when a CH_2Cl_2 solution of **3** and **68a** was used, a 85:15 mixture of **73a**/***epi*-73a** was obtained in excellent conversion (>98%), whereas no reaction was observed when a THF solution of **3** and **68a** was treated with this base (**Table 2.1, entry 2**). Changing DABCO in THF by DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) in this solvent, also kept the starting materials unaltered (**Table 2.1, entry 3**). However, the same reaction in the presence of DMAP in THF, gave a 86:14 mixture of **73a** and its C-2 epimer ***epi*-73a** in 62% conversion (**Table 2.1, entry 4**). The ratio of epimers formed was determined by integration of well differentiated signals ($\delta_{H\text{-}2}$ (**73a**) = 5.90 ppm; $\delta_{H\text{-}2}$ (***epi*-73a**) = 6.08 ppm) in the ^{1}H-NMR spectrum of the crude reaction mixture. In order to obtain the dioxolane derivatives **73** with better diastereoselectivity and conversion, while the base was kept (DMAP) a series of solvents was screenned to see their influence in the reaction course. Thus, when DMAP was the catalyst in CH_3CN a 63:37 mixture of **73a**/***epi*-73a** with a slightly better conversion of 70% (**Table 2.1, entry 5**) resulted. With the change to CH_2Cl_2 as solvent, an improvement of the diastereoselectivity (up to a 90:10 mixture of **73a**/***epi*-73a**) was observed as well as an increase of the conversion (>98%) (**Table 2.1, entry 6**). When a protic solvent such as MeOH was used, exclusively the mono-MBH adduct (**Table**

2.1, entry 7) resulted in high conversion (>98%) as a 60:40 mixture of diastereoisomers **69a**/***epi*-69a**. The influence of the inorganic base Cs_2CO_3 was also evaluated. As it has been previously described, the use of Cs_2CO_3 in MeOH afforded a mixture of the mono and the bis-MBH adducts. Thus, we used this base with a different solvent than MeOH in order to obtain exclusively the dioxolanes. Unfortunately, no conversion was observed probably due to the low solubility of the base in the chlorinated solvent (**Table 2.1, entry 8**).



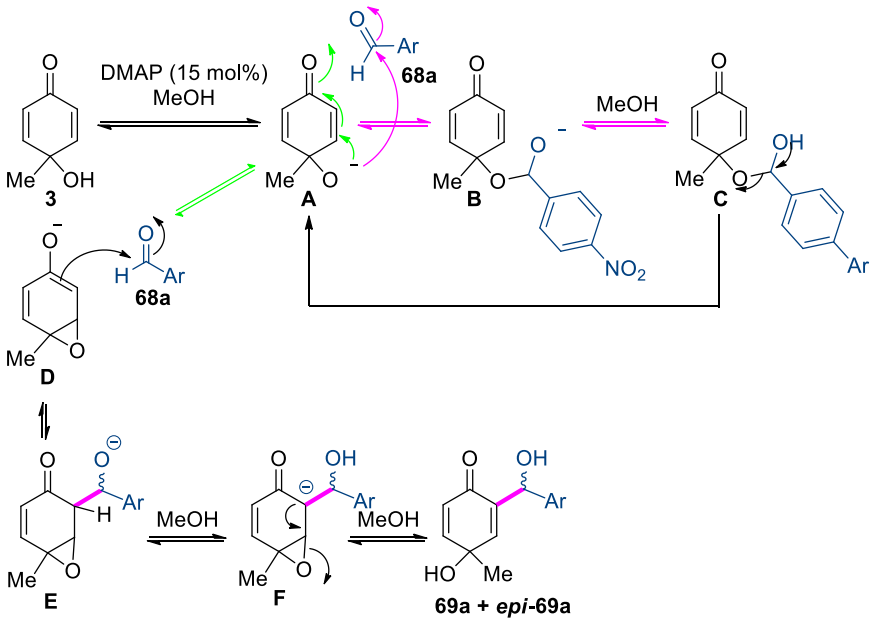
Entry	Base	Solvent	Conversion	Product (*d.r.*)[a]
1	DABCO	CH_2Cl_2	>98	**73a**/***epi*-73a** (85:15)
2	DABCO	THF	-	No reaction
3	DBU	THF	-	No reacction
4	DMAP	THF	62	**73a**/***epi*-73a** (86:14)
5	DMAP	CH_3CN	70	**73a**/***epi*-73a** (63:37)
6	DMAP	CH_2Cl_2	>98	**73a**/***epi*-73a** (90 (67)[b]:10 (3)[b])
7	DMAP	MeOH	>98	**69a**/***epi*-69a** (60:40)
8	Cs_2CO_3	CH_2Cl_2	-	No reaction

[a] Diastereomeric ratio measured by ^{1}H-NMR spectroscopy; [b] % Isolated yield of the separated diastereoisomer.

Table 2.1

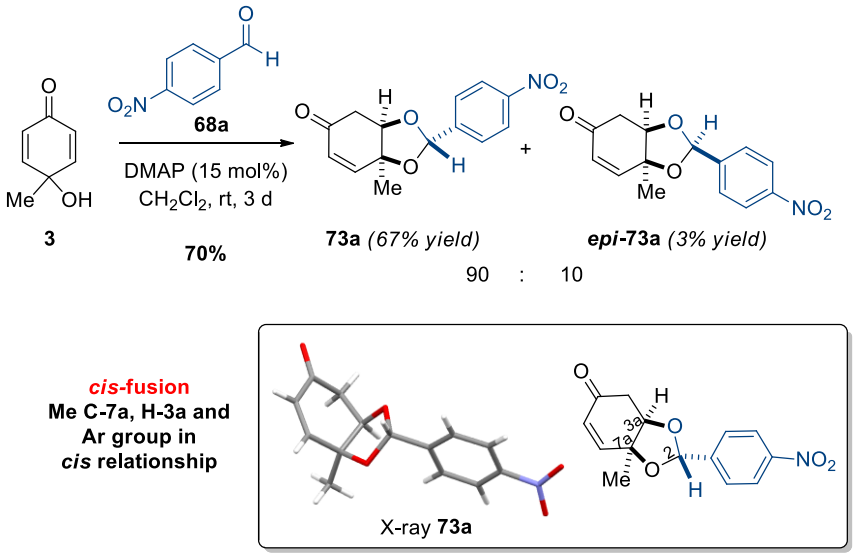
In summary, as was evident from the results included in **Table 2.1**, the use of DMAP with THF, CH_3CN and CH_2Cl_2 afforded dihydrobenzo[*d*][1,3]-dioxol-5[7aH]-ones **73a** and ***epi*-73a** and only when MeOH was the solvent, the formation of MBH adducts **69a** and ***epi*-69a** was observed. As shown in **Scheme 2.54**, it could be explained by the ability of MeOH to protonate

the acetalic intermediate alkoxide **B** formed after the 1,2-addition of *p*-quinol alkoxide **A** over the carbonilic carbon of aldehyde **68a**. The hemiacetal **C** could then revert to the intermediate alkoxide of *p*-quinol **A**, favoring the intramolecular oxa-Michael reaction **D** followed by the 1,2-addition to the aldehyde **E** which evolves to the Baylis-Hillman adducts **69a/*epi*-69a**, after epoxide ring opening favored by protonation with MeOH.



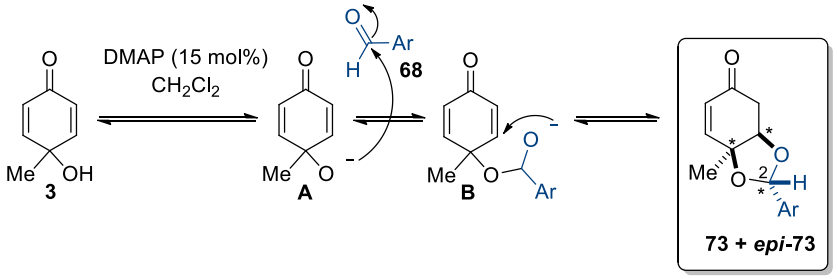
Scheme 2.54

The best experimental conditions for the synthesis of the fused dioxolanes was the combination of DMAP/CH_2Cl_2. The 90:10 mixture of epimers formed could be separated to isolate each one diastereomerically pure in 67% (**73a**) and 3% (***epi*-73a**) yields, respectively (**Scheme 2.55**). The unequivocal structure of the major diastereoisomer **73a** was confirmed by X-Ray diffraction, which evidenced the *cis*-fusion of the rings and the *cis*-relative relationship between the methyl group at C-7a, H-3a and the *p*-nitrophenyl substituent at C-2 (**Scheme 2.55**).



Scheme 2.55

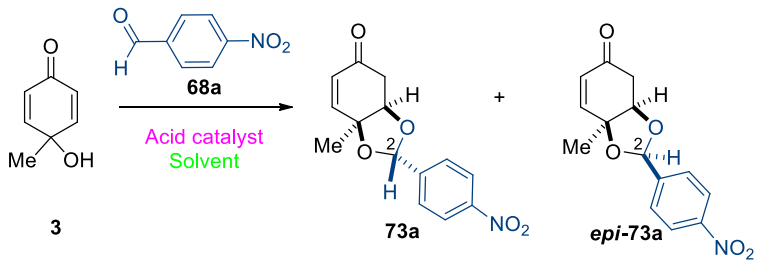
The formation of dihydrobenzo[1,3]-dioxolan-5-ones **73** could be explained by the mechanism indicated in **Scheme 2.56**. In the first step, the alkoxide **A**, formed by deprotonation of the hydroxyl group of quinol **3** by the tertiary nitrogen base, must attack the aldehyde through an acetalization process, giving the intermediate **B**. The acetalic anion intermediate **B** undergoes an intramolecular oxa-Michael addition on one of the two prochiral β carbons of quinol. This attack must occur from the face of the *p*-quinol **3** containing the hydroxy group to give the major diastereoisomer. In these three steps three new stereogenic centers were formed with a high diastereoslectivity since only two diastereoisomers (epimers at C-2 in a 90:10 ratio) were formed. The detailed stereochemical course of the process will be explained later.



Scheme 2.56

With the aim of achieving the synthesis of these fused dioxolanes in better diastereoselectivity and yield we further screened the reaction in acidic conditions as the

synthesis of a few analogues of 1,3-dioxolanes had been already reported in the literature.[21] Thus, the study was again carried out using *p*-quinol **3** and *p*-nitrobenzaldehyde **68a** as a model of aromatic aldehyde (**Scheme 2.57**).



Conditions	Conversion	*dr* **73a**:***epi*-73a**[a] (Yield%)
$TiCl_4$ (1.2 equiv), CH_2Cl_2	No reaction	-
TSA (10 mol%), THF	77	62:38

[a] Diastereomeric ratio measured by ^{1}H-NMR spectroscopy

Scheme 2.57

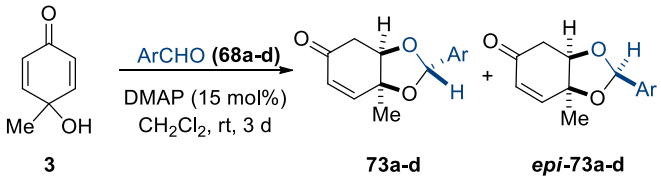
As shown in **Scheme 2.57**, when 1.2 equivalents of a Lewis acid such as $TiCl_4$ were added to a CH_2Cl_2 solution of **3** and **68a**, no reaction took place while 10 mol% of a Brønsted acid such as *p*TSA (*p*-toluene sulfonic acid), gave a 62:38 mixture of **73a**/***epi*-73a** in a 77% conversion.

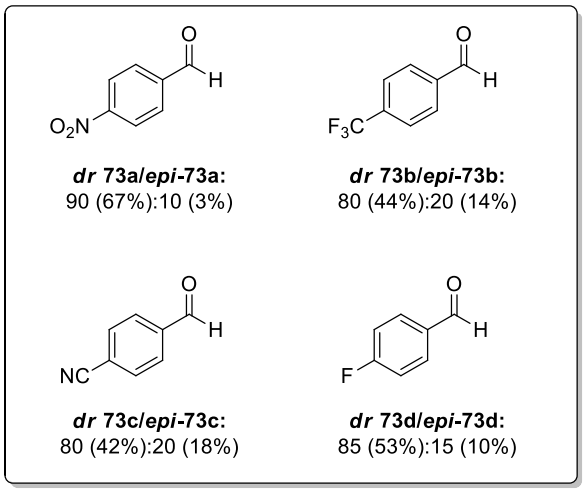
Reaction of *p*-quinol 3 with differently substituted aromatic aldehydes.

If we compare the results obtained when a basic catalyst or an acid catalyst were used in the model reaction, we could conclude that the best experimental conditions to synthesize the 1,3-dioxolanes (good yield and diastereoselectivity) consisted on 15 mol% of DMAP as base and CH_2Cl_2 as solvent at room temperature. With these conditions in hand, we decided to study the scope of this reaction between *p*-quinol **3** and aromatic aldehydes **68** where either the electronic character of the substituent or its relative position on the aromatic ring could influence the results

Firstly, aromatic aldehydes with electron withdrawing substituents were tested. For comparison, the result previously obtained with *p*-nitrobenzaldehyde **68a** is included in **Scheme 2.58**. Thus, the use of *p*-NO_2 group afforded a 90:10 mixture of **73a**/***epi*-73a** with 67 and 3% isolated yield respectively. The *p*-CF_3 substituted aromatic aldehyde gave a 80:20 mixture of diastereoisomers **73b** and ***epi*-73b** from which **73b** was isolated pure in 44% yield

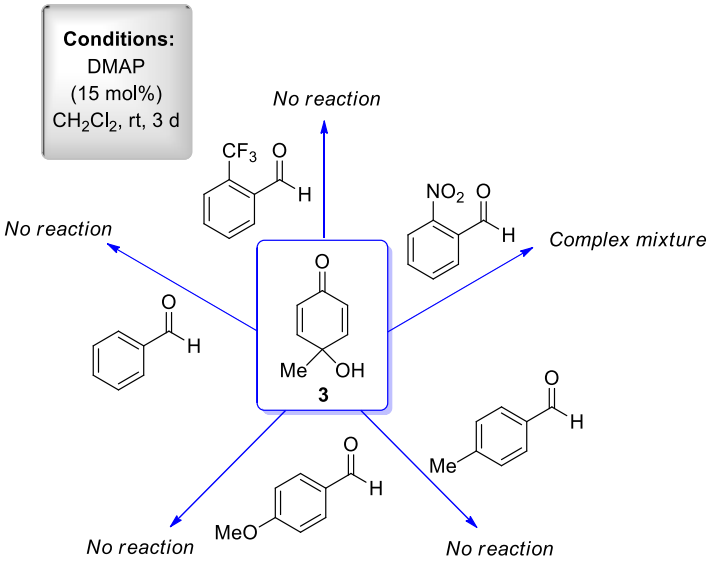
and ***epi*-73b** in 14% yield. A similar diastereoselectivity was observed in the DMAP catalyzed reaction between *p*-quinol **3** and *p*-cyanobenzaldehyde **68c**, affording a 80:20 mixture of **73c/*epi*-73c** isolated in 42 and 8% yield respectively. The use of *p*-fluorobenzaldehyde **68d** allowed the diastereoselective formation of derivatives **73d/*epi*-73d** in a 85:15 ratio and 53 and 10% isolated yields respectively.





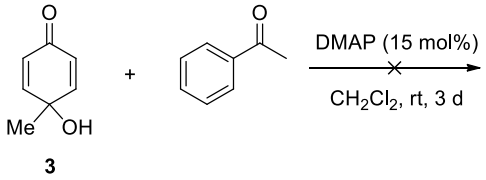
Scheme 2.58

The influence of the relative position of the substituent at the aromatic aldehyde was also evaluated under DMAP catalyzed conditions in CH_2Cl_2. Thus, an *ortho* disposition of a CF_3 in the aromatic aldehyde resulted in the lack of reactivity (**Scheme 2.59**). A complex reaction mixture resulted in the case of reaction of *p*-quinol **3** with *o*-nitrobenzaldehyde (**Scheme 2.59**). This lack of reactivity could be a consequence of the steric hindrance produced by the substituent in the *ortho* position during the attack of the tertiary alcoxide derived from quinol **3**. Thus, we could conclude that the synthesis of fused dioxolanes **73** is highly dependent on the position of the substituent on aldehyde having electron withdrawing substituents. When an electron donating group such as Me or OMe was present in the aromatic aldehyde, the dihydrobenzodioxolones derivatives **73** were not observed (**Scheme 2.59**) and the same happens when no substituent is present in the aromatic ring of the aldehyde (**Scheme 2.59**).



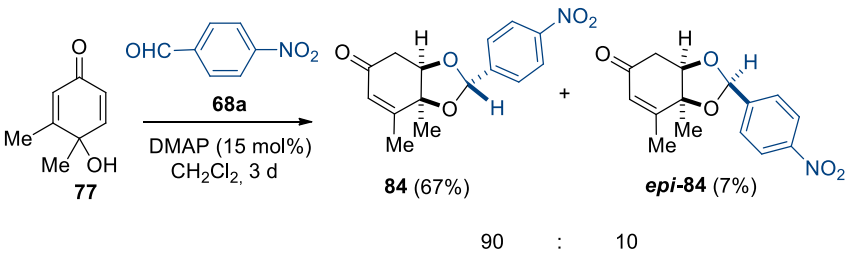
Scheme 2.59

The use of ketones instead of aldehydes did not afford the product, recovering the starting material unaltered in the reaction of *p*-quinol **3** with acetophenone in the presence of DMAP and CH_2Cl_2 (**Scheme 2.60**).



Scheme 2.60

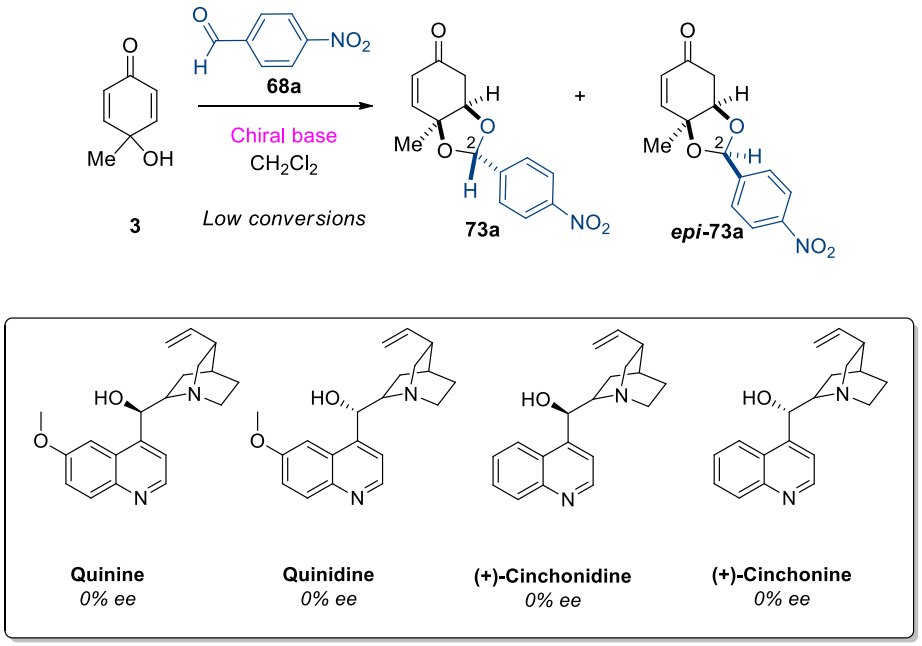
Then, the reaction of 3-methyl-*p*-quinol **77** with *p*-nitrobenzaldehyde **68a** was evaluated in the presence of DMAP as catalyst and CH_2Cl_2 as solvent. The 1,3-dioxolane **84** was formed in good yield and diastereoselectivity (90:10, **84/*epi*-84**). Both diastereoisomers were isolated pure in 67 and 7%, respectively In this case, the intramolecular oxa-Michael addition of the hemiacetal derived alkoxide took place through the more electrophilic unsubstituted double bond of the cyclohexadienone moiety, giving the all *cis*-substituted bicyclic structure **84** as major (**Scheme 2.61**).



Scheme 2.61

Enantioselective version of the synthesis of 1,3-dioxolanes from aromatic aldehydes.

In order to achieve the synthesis of 1,3-dioxolanes from aromatic aldehydes enantioselectively, we decided to study the model of *p*-quinol **3** with *p*-nitrobenzaldehyde **68a**, in the presence of different tertiary chiral amines, which could catalyze the process (**Scheme 2.62**).

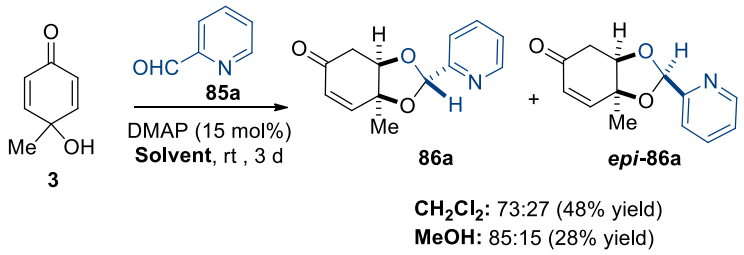


Scheme 2.62

Thus, reaction of *p*-nitrobenzaldehyde **68a** and *p*-quinol **3** was carried out in CH_2Cl_2 solution, by adding different enantiopure alkaloids such as Quinine, Quinidine, (+)-Cinchonidine and (+)-Cinchonine. In all cases, low conversions were obtained in a racemic manner (enantiomeric excess was measured by HPLC with a chiral column (IB-0.6ml/min-10% isopropanol-60).

Reactions of p-quinols with heteroaromatic aldehydes.

We also checked the behavior of different heteroaromatic aldehydes in the base catalyzed reactions with *p*-quinol **3**. Thus, when a mixture of pyridine-2-carboxaldehyde **85a** and *p*-quinol **3** was treated with DMAP (15 mol%) in CH_2Cl_2 solution, a 73:27 mixture of dioxolane **86a** and its C-2 epimer ***epi*-86a** was formed in a 48% yield (**Scheme 2.63**). When the solvent was changed to MeOH, a 28% yield for a 85:15 mixture of C-2 epimers **86a/*epi*-86a** was obtained (**Scheme 2.63**).



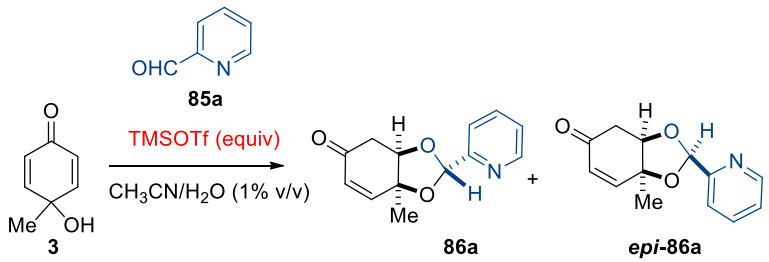
Scheme 2.63

The use of TMSOTf had been reported to act as a Lewis acid catalyst increasing the electrophilic character of pyridine-2-carboxaldehyde as acceptor in Baylis-Hillman reactions[62] leading to the formation of indolizidines. Intrigued by these results, we checked the reaction of **3** with pyridine-2-carboxaldehyde **85a** in the presence of TMSOTf using CH_3CN/H_2O (1 % v/v) as solvent. Under these conditions, the formation of the [1,3]-dioxolanes **86a** and ***epi*-86a** at C-2 was observed as the only reaction products. The relative ratio of both epimers was slightly different depending on the amounts of TMSOTf of the different experiments and the number of equivalents of TMSOTf was critical to reach a good conversion as shown in **Table 2.2**.

No significant reaction was observed in the absence of TMSOTf (**Table 2.2, entry 1**) since after 5 days only a 8% conversion resulted. The desired products **86a** and ***epi*-86a** were formed in a 55:45 ratio. When 0.5 equivalents of TMSOTf were added, after 5 days of reaction, a 28% of conversion and a 56:44 mixture of **86a**/***epi*-86a** (**Table 2.2, entry 2**) were observed.

[62] Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604.

These two results suggested that the uncatalysed reaction occurred mainly and the TMSOTf was only slightly improving the conversion. The increase to 1 equivalent of TMSOTf allowed reaching a 68% conversion and 63:37 **(86a/*epi*-86a)** of diastereoselectivity after 4 days (**Table 2.2, entry 3**). The increase to 2 and 3 equivalents of TMSOTf inverted the diastereoselectivity obtaining a 50% conversion and a 30:70 mixture of **86a/*epi*-86a** with 2 equivalents (**Table 2.2, entry 4**) and 86 % conversion and a 17:83 ratio **(86a/*epi*-86a)** with 3 equivalents (**Table 2.2, entry 5**). When an excess of 10 equivalents of TMSOTf was added, the mixture decomposed (**Table 2.2, entry 6**). A possible explanation of the inversion of the diastereoselectivity observed will be detailed in next section.

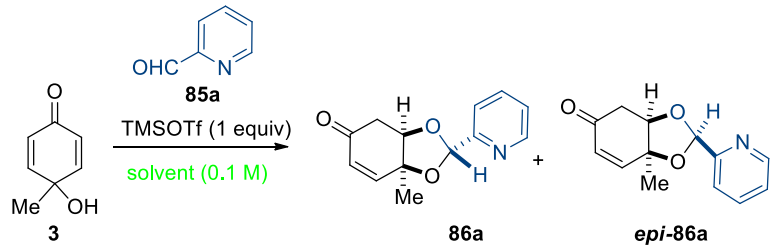


Entry	TMSOTf (equiv)	Time	Conversion	**86a**/***epi*-86a** (*d.r.*)[a]
1	-	5 d	8	55:45
2	0.5	5 d	28	56:44
3	1	4 d	68	63:37
4	2	2 d	50	30:70
5	3	2 d	86	17:83 (33)[b]
6	10	5 d	-	-

[a] Diastereomeric ratio measured by ^{1}H-NMR spectroscopy ; [b] Isolated global yield

Table 2.2

We next screened different solvents to check if it was possible to improve these results. Unfortunately, the use of other solvents did not afford better results. Thus, the reaction between *p*-quinol **3** and pyridine carboxaldehyde with 1 equivalent of TMSOTf in MeOH or CH_2Cl_2 resulted in 65:35 and 41:59 mixtures of **86a/*epi*-86a** and conversions of 50 and 70 respectively (**Table 2.3, entries 1 and 2**). The use of THF as solvent did not result in the formation of desired products as the starting materials were recovered unaltered (**Table 2.3, entry 3**).



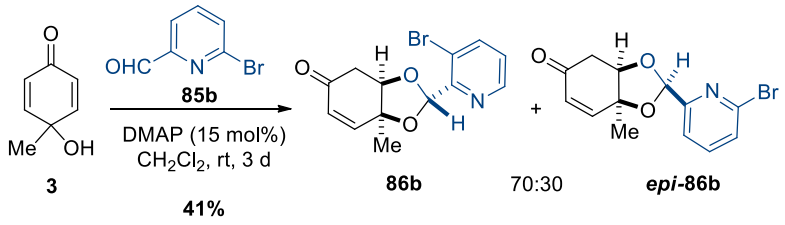
Entry	Solvent	Time	Conversion	**86a**/***epi*-86a** (*d.r.*)[a]
1	MeOH	5 d	50	65:35
2	CH_2Cl_2	5 d	70	41:59
3	THF	5 d	-	-

[a] Diastereomeric ratio measured by ^{1}H-NMR spectroscopy

Table 2.3

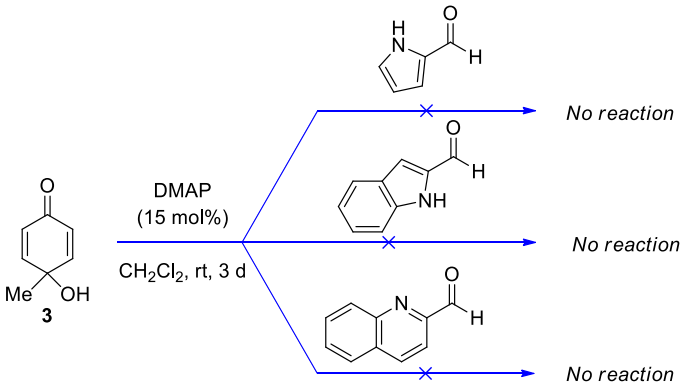
The formation of bicyclic 1,3-dioxolanes **86a** and ***epi*-86a** with TMSOTf (3 equiv) in CH_3CN /H_2O afforded only a 33% isolated yield, which was not useful from the preparative point of view but it is worth to mention the inversion of the diastereoselectivity observed, in comparison with the DMAP catalyzed process.

Differently substituted 2-pyridine carboxaldehyde such as 6-bromopyridine-2-carboxaldehyde **85b** reacted under basic catalyzed conditions (DMAP, CH_2Cl_2), leading to a 70:30 mixture of **86b** and ***epi*-86b** in a moderate 41% yield (**Scheme 2.64**).



Scheme 2.64

Reaction with π-excedent heteroaromatic aldehydes such as pyrrole-2-carboxaldehyde, indole-2-carboxaldehyde or quinoline-2-carboxaldehyde did not occur with *p*-quinol **3** in the presence of DMAP, thus evidencing that the base catalyzed formation of the acetals only occurred when the heteroaromatic substituent is an electron withdrawing group, which increases the electrophilic character of the aldehyde (**Scheme 2.65**).

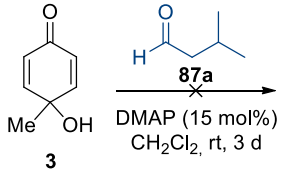


Scheme 2.65

We also checked the reaction of *p*-quinol **3** with the aromatic aldehyde **68a** in the presence of TMSOTf as catalyst. In this case a complex mixture was obtained.

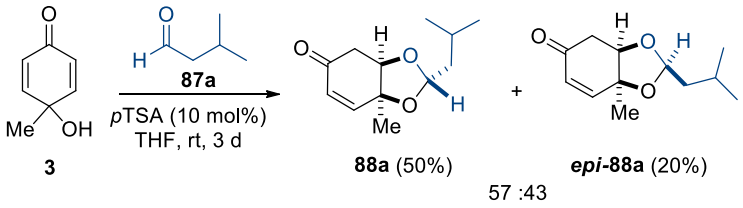
Reactions of p-quinols with aliphatic aldehydes.

More challenging aliphatic aldehydes were next screened in the reaction of *p*-quinol **3**. Under basic conditions (DMAP, CH_2Cl_2), 3-methyl butanal **87a** did not react with *p*-quinol **3** (**Scheme 2.66**). This result was not surprising since the base catalyzed formation of the acetals only occurred with highly reactive electron withdrawing substituted benzaldehydes.



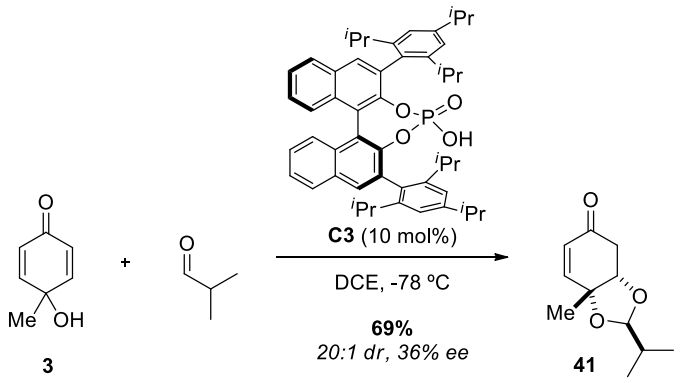
Scheme 2.66

The use of an acid catalyst such as Amberlyst-15 or H_2SO_4 (20 mol% in an aqueous solution) was reported to catalyze the reaction of *p*-quinols with aldehydes to give the *cis*-bicyclic dioxolanes with diastereoselectivites below 60:40.[21a] We tested similar acidic conditions (*p*TSA (10 mol%), for the reaction between **3** and **87a**, and a 57:43 mixture of epimeric hydrobenzodioxolanones **88a** and ***epi*-88a** was formed, from which both were isolated pure in 50% and 20% yield, respectively (**Scheme 2.67**).



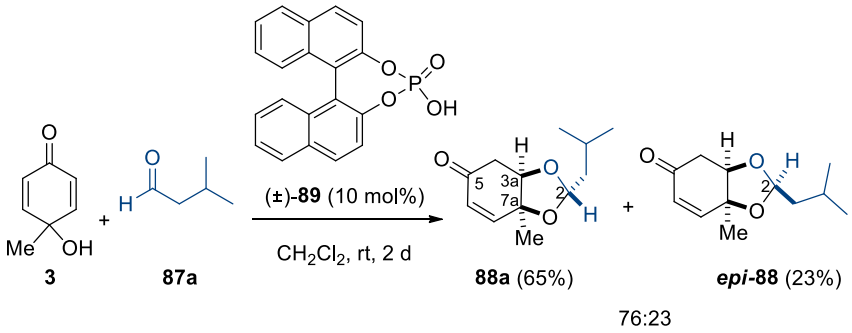
Scheme 2.67

With the aim of increasing the diastereoselectivity and the yield of this reaction, we next tested a different acid catalyst. The successful asymmetric reaction of *p*-peroxyquinols with aliphatic aldehydes catalyzed by enantiopure phosphoric acid derivatives developed by the group of Rovis,[45] prompted us to look at the effect of this Brønsted acid in the reaction of *p*-quinol **3**. As it was mentioned before, during the development of this work, another publication by Rovis appeared. In this work, the use of enantiopure phosphoric acids as catalysts in the reaction of *p*-quinols with aldehydes and imines was reported.[21b] Only moderate enantiomeric excess were achieved being the best one the example shown in **Scheme 2.68**.



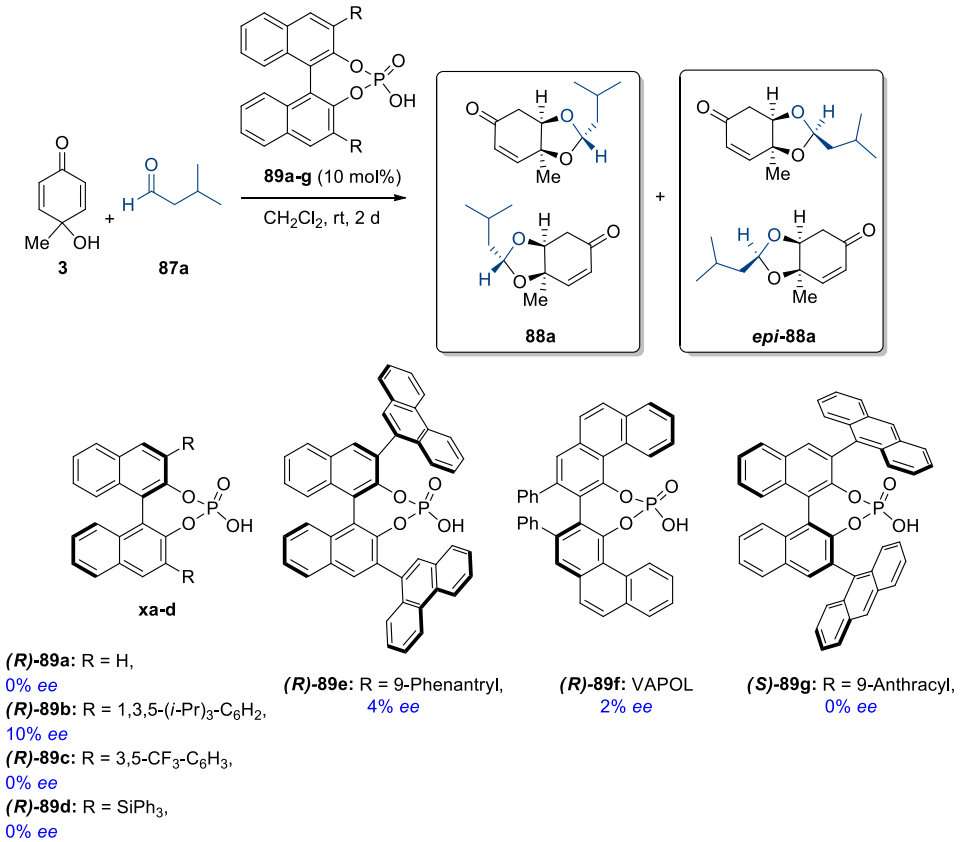
Scheme 2.68

As it is shown in **Scheme 2.69**, we used racemic BINOL derived phosphoric acid **(±)-89** to catalyze the reaction between *p*-quinol **3** and 3-methyl butanal **87a**. A 76:23 mixture of diastereomeric hydrobenzo-[1,3]-dioxol-5(7aH)-ones **88a** and ***epi*-88a** resulted, which could be isolated pure in 65 and 23% yield, respectively.



Scheme 2.69

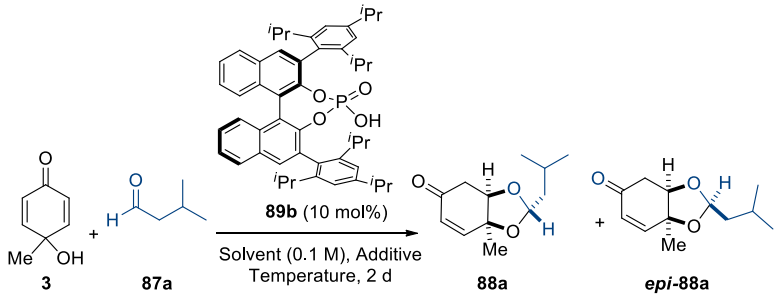
With this result in hand, we decided to study the enantioselective version of this reaction using different chiral phosphoric acids as catalyst (**89a-g**), with the aim of achieving the desymmetrization of the 2,5-cyclohexadienone scaffold to obtain mainly one of the two enantiomers of each diastereoisomers **88a** and ***epi*-88a** (**Scheme 2.70**).



Scheme 2.70

The screening started using a 10 mol% of phosphoric acids **89a-g** in CH_2Cl_2 (0.1 M) at room temperature for the reaction between *p*-quinol **3** and 3-methylbutanal **87a** (**Scheme 2.70**). Among all the chiral phosphoric acids tested **89a-g** only **89b** seemed to enantioselectively induce the reaction though with a poor 10% enantiomeric excess. The

enantiomeric ratio was determined by HPLC (IC-0.5 ml/min–3% isopropanol–50 min). Most of the phosphoric acids are commercially available and accessible. Only catalyst **89e** was synthetized following the procedure reported by Hu *et al.*[63] With the catalyst **89b**, we decided to study the reaction modifying different experimental parameters such as the solvent and the temperature as well as using molecular shieves as additive (**Table 2.4**). The best result obtained was using CH_2Cl_2 as solvent and activated 4Å molecular shieves (**Table 2.4, entry 3**), obtaining **88a** in a 20% enantiomeric excess.



Entry	Solvent	Additive	Temperature	*ee* % (**88a**)[a]
1	CH_2Cl_2	-	rt	10
2	CH_2Cl_2	-	-20°C	12
3	CH_2Cl_2	4Å MS	rt	20
4	Toluene	-	rt	0
5	CH_3CN	-	rt	16

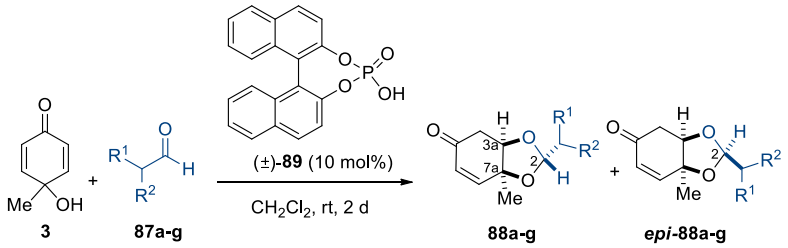
[a] Enantiomeric ratio measured by HPLC analysis (IC-0.5 ml/min–3%^{i}PrOH/50 min).

Table 2.4

Reaction of *p*-quinol 3 with aliphatic aldehydes 87a-g.

At this point, and based on the difficulty found to achieve the enantioselective synthesis of bicyclic dioxolanes **88** and their C-2 epimers, we decided to study the scope of this reaction using racemic BINOL phosphoric acid **(±)-89** as catalyst (**Scheme 2.71**).

[63] Hu, W.; Zhou, J.; Xu, X.; Liu, W.; Gong, L. *Org. Synth.* **2011**, *88*, 406.



Scheme 2.71

The results of the BINOL phosphoric acid derivative catalyzed reactions of *p*-quinol **3** with different aliphatic aldehydes **87a-g** are recovered in **Figure 2.3**. Reaction of 3-methylbutanal **87a** with **3** gave a 76:24 *dr* and 65 and 23% isolated yield of **88a** and ***epi*-88a** respectively. Better diastereoselectivity (89:11) was obtained in the analogue reaction of isobutyraldehyde **87b**, affording 83 and 4% isolated yield of **88b** and ***epi*-88b** respectively. The reaction of *p*-quinol **3** and cyclohexanecarbaldehyde **87c** afforded epimers **88c** and ***epi*-88c** isolated in a 83:17 ratio in 81 and 16% yield respectively. Similar results were obtained when 2-phenylacetaldehyde **87d** reacted with *p*-quinol **3**. Thus, a 87:13 mixture of epimers **88d/*epi*-88d** was obtained and they were isolated in 86 and 8% yield. The use of acetaldehyde **87e** gave a moderate diastereoselectivity (67:33) with an isolated yield of **88e** (the major diastereoisomer) of 41%. Its epimer, ***epi*-88e**, was not isolated after purification by flash column chormatography, therefore, its yield was calculated by ^{1}H-NMR of the reaction crude (10%). Similar diastereoselectivities were obtained in the case of propionaldehyde **87f** and butyraldehyde **87g** (76:24 in both cases) with 50 and 75% yields of **88f** and **88g** and 15 and 21% of ***epi*-88f** and ***epi*-88g** respectively.

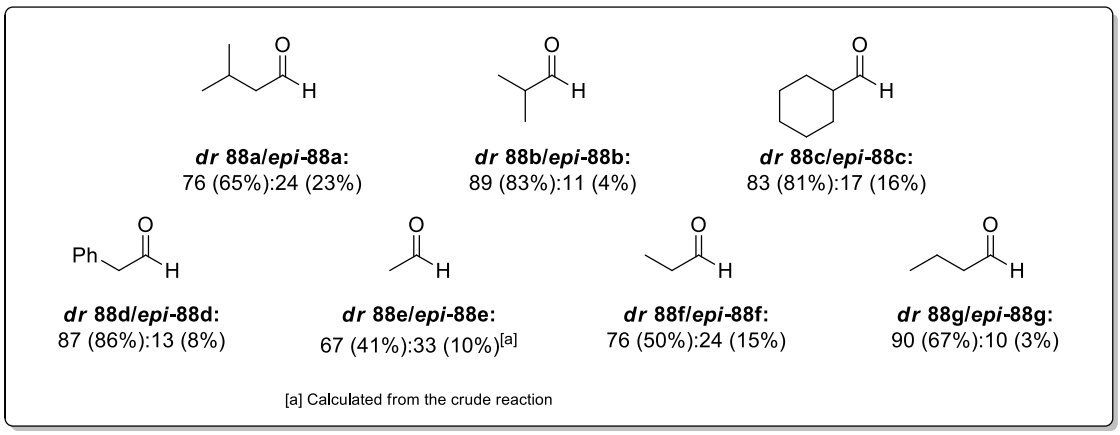
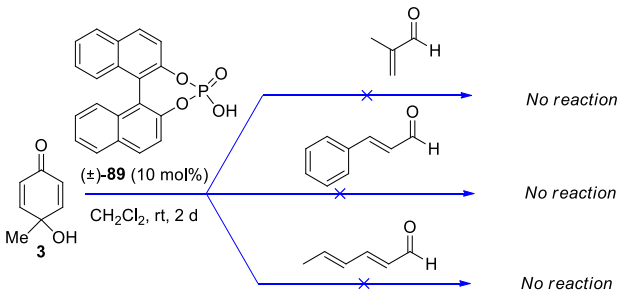


Figure 2.3

α,β-Unsaturated aldehydes such as methacrolein, cinnamaldehyde or 2,4-hexadienal did not react under these conditions (**Scheme 2.72**).



Scheme 2.72

Structural assignment of dihydrobenzo[d][1,3]-dioxol-5(7aH)-ones.

The structure and relative stereochemistry of all the hydrobenzodioxol-5(7aH)-ones **73**, **84**, **86**, and **88** and their C-2 epimers obtained, was established on the base of their spectroscopic parameters, mainly ^{1}H-NMR data and NOESY experiments. Moreover, the stereochemical assignment of the diastereoisomers, was based on the comparison of their ^{1}H-NMR parameters with those of **73a**, whose structure had been unequivocally established by X-Ray (**Figure 2.4**). As it can be seen in the X-Ray structure of **73a**, the major diastereoisomer resulting from the reaction between *p*-quinol **3** and *p*-nitrobenzaldehyde **68a** under DMAP/CH_2Cl_2 conditions situates the methyl group at C-7a, the substituent at C-2 and the hydrogen at C-3a in relative *cis* disposition.

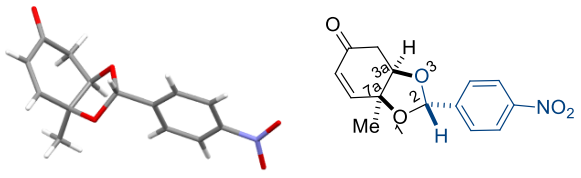


Figure 2.4

We must consider 3 different possibilities for minor diastereoisomer: the epimer at C-2, the *trans*-fused dioxolane keeping the same relative configuration at C-2 than the major diastereoisomer and the *trans*-fused dioxolane with the opposite configuration at C-2 (**Figure 2.5**).

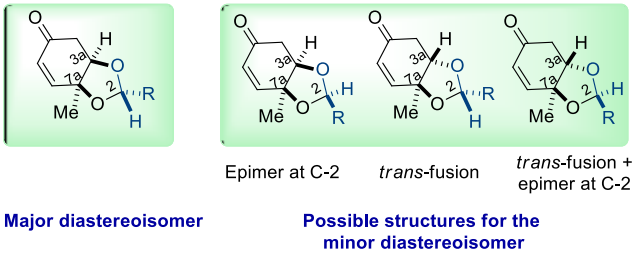
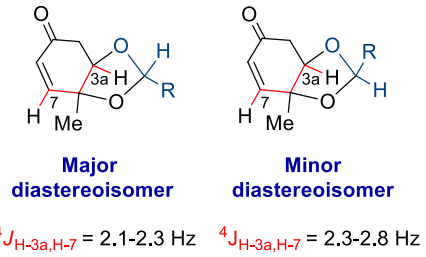


Figure 2.5

The *trans*-fusion of the dioxolane ring could be disregarded on the base of the following spectroscopic parameters. First, a *W*-type coupling between H-7 and H-3a was observed in the ^{1}H-NMR spectrum in both the major and minor epimers. One of the most significant features, indicated in **Table 2.5**, is the appearance of a long-range coupling constant between the olefinic proton H-7 of the cyclohexenone moiety and H-3a of $^{4}J_{HH} \approx 2$ Hz in both diastereomers of the hydrobenzodioxol-5(7aH)-ones. This *W*-type coupling is only possible if H-3a is situated in a pseudo equatorial disposition, possible only in a *cis* ring junction (**Table 2.5, entries 1-6 and 8-14**). In the case of 3-methyl-substituted dioxolane **84a**, the ^{1}H-NMR spectra does not show any *W*-type constant in H-3a because, in this case, H-7 has been replaced by a methyl group (**Table 2.5, entry 7**).

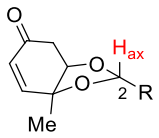


Entry	Major diastereoisomer	$^{4}J_{H3a,\,H7}$ (Hz)	Minor diastereoisomer	$^{4}J_{H3a,\,H7}$ (Hz)
1	**73a**	2.1	***epi*-73a**	2.4
2	**73b**	2.1	***epi*-73b**	2.3
3	**73c**	2.3	***epi*-73c**	2.8
4	**73d**	2.1	***epi*-73d**	2.3
5	**86a**	2.2	***epi*-86a**	2.2
6	**86b**	2.1	***epi*-86b**	2.3
7	**88a**	2.2	***epi*-88a**	2.4
8	**88b**	2.2	***epi*-88b**	2.4
9	**88c**	2.2	***epi*-88c**	2.3
10	**88d**	2.2	***epi*-88d**	2.4
11	**88e**	2.2	***epi*-88e**	2.7[a]
12	**88f**	2.2	***epi*-88f**	2.6
13	**88g**	2.1	***epi*-88g**	2.4

[a] Calculated by ^{1}H-NMR spectroscopy of the crude reaction.

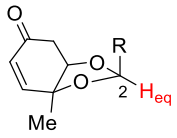
Table 2.5

Another significant feature to assign the structure of both epimers is the difference of the chemical shift of H-2 in each one in the ^{1}H NMR spectra. In the major one (**73**, **84**, **86** and **88**), having the C-2 aryl or alkyl substituent in the equatorial disposition, the axial H-2 appeared at higher field than in the minor epimers where the H-2, situated in the equatorial disposition, appeared at lower field (**Table 2.6, entries 1-14**).



Major diastereoisomer

R = Ar: $\delta_{H\text{-}2}$ = 5.81-5.90
R = Alkyl: $\delta_{H\text{-}2}$ = 4.70-4.97



Minor diastereoisomer

R = Ar: $\delta_{H\text{-}2}$ = 5.80-6.08
R = Alkyl: $\delta_{H\text{-}2}$ = 4.86-5.33

Entry	Major diastereoisomer	$\delta_{H\text{-}2}$ (ppm)	Minor diastereoisomer	$\delta_{H\text{-}2}$ (ppm)
1	**73a**	5.90	***epi*-73a**	6.08
2	**73b**	5.88	***epi*-73b**	6.06
3	**73c**	5.85	***epi*-73c**	6.04
4	**73d**	5.81	***epi*-73d**	5.99
5	**84a**	5.81	***epi*-84a**	5.80
6	**86a**	5.87	***epi*-86a**	6.08
7	**86b**	5.81	***epi*-86b**	5.98
8	**88a**	4.97	***epi*-88a**	5.17
9	**88b**	4.70	***epi*-88b**	4.86
10	**88c**	4.67	***epi*-88c**	4.86
11	**88d**	5.18	***epi*-88d**	5.33
12	**88e**	5.06	***epi*-88e**	5.22[a]
13	**88f**	4.90	***epi*-88f**	5.09
14	**88g**	4.93	***epi*-88g**	5.13

[a] Calculated by ^{1}H-RMN spectroscopy of the crude reaction.

Table 2.6

Finally, the stereochemistry of the minor epimers was also corroborated by bidimensional NOESY experiments for derivatives ***epi*-86b** (resulting in the reaction with 6-bromopyridyl-2-carboxaldehyde) and ***epi*-88a** (resulting in the reaction with 3-methylbutanal). In the case of ***epi*-86b** a NOE effect was observed between **H-3a** (δ = 4.45 ppm) and the **Me** group at C-7a (δ = 1.59 ppm) and **H-3a** and **H-2** (δ = 5.98 ppm). In the diastereoisomer ***epi*-88a** there is also a NOE effect between **H-3a** (δ = 4.19 ppm) and **H-2** (δ = 5.17 ppm) was observed (**Figure 2.6**).

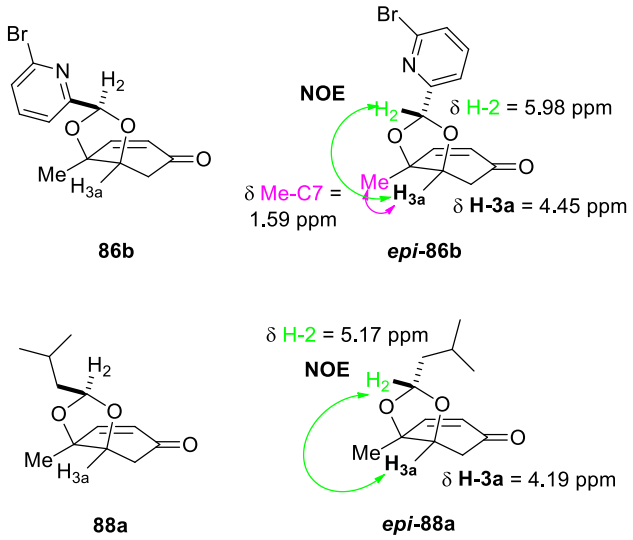
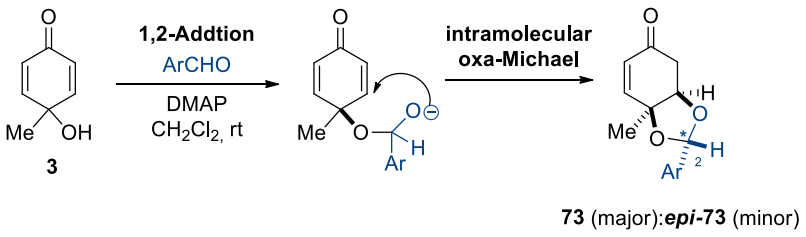


Figure 2.6

Mechanism and stereochemistry for the formation of dihydrobenzodioxolones.

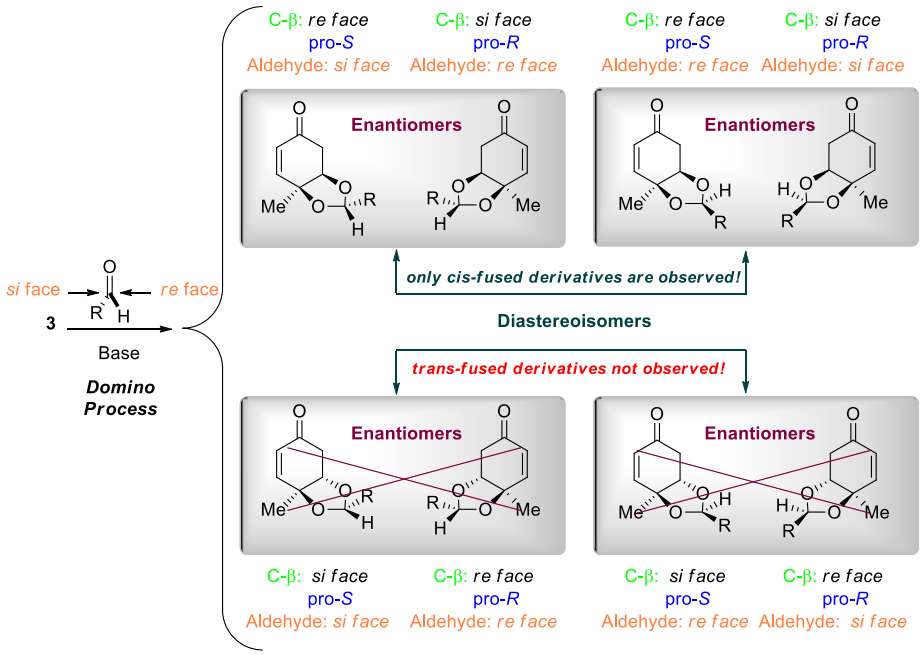
Once the stereochemical map of the addition of a nucleophile to the prochiral 2,5-cyclohexadienone has been explained (in this Chapter), it is convenient to review the stereochemistry in the synthesis of the dihydrobenzo[1,3]dioxol-5(7aH)-ones, which incorporate a new stereogenic center proceding from the aldehyde.

As previously mentioned, the mechanism of the formation of the dihydrobenzo-[1,3]-dioxol-5(7aH)-ones by base catalyzed reaction between *p*-quinols and aldehydes involves a 1,2-addition of the C-4 hydroxy group of the *p*-quinol **3**, acting as a nucleophile, to the aldehyde, followed by an intramolecular oxa-Michael addition of the intermediate hemiacetal anion to the cyclohexadienone moiety to give a *ca* 80:20 mixture of diastereoisomeric dihydrobenzo-[1,3]-dioxol-5(7aH)-ones **73** and ***epi*-73** (**Scheme 2.73**).



Scheme 2.73

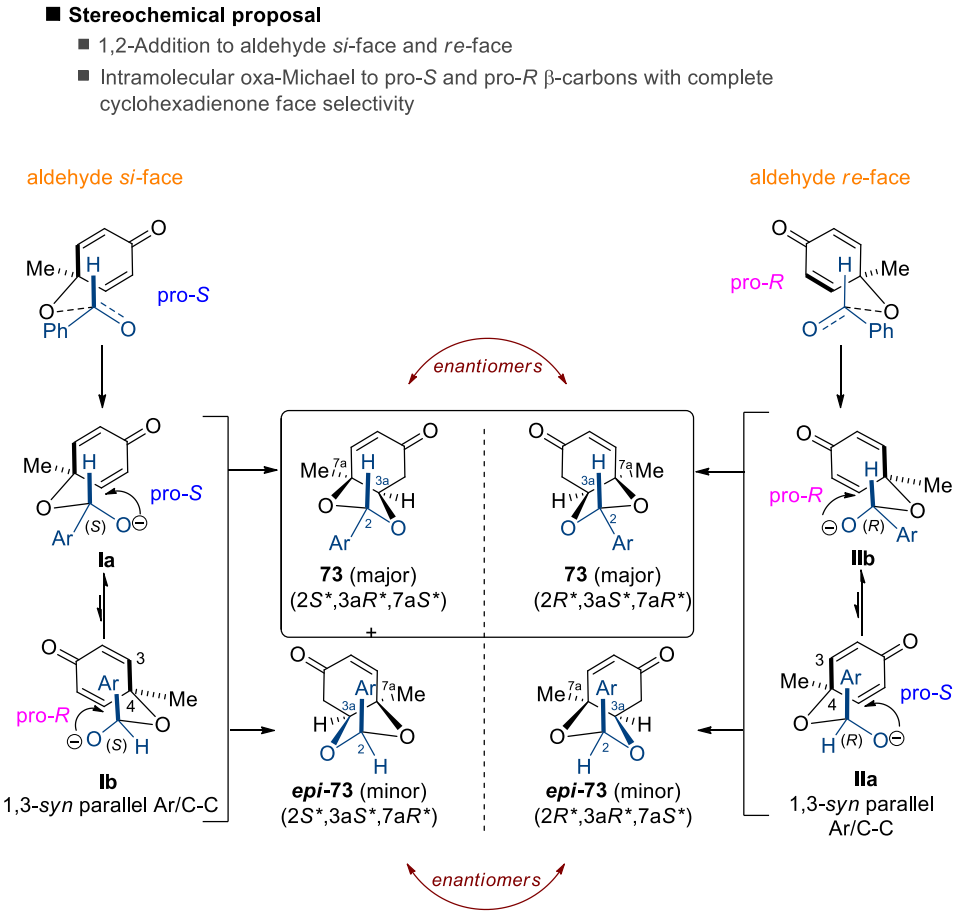
In this domino process there are several stereochemical aspects that should be considered. The initial 1,2-addition step of the tertiary OH to the carbonyl aldehyde generates a new stereocenter as a consequence of the attack of the *p*-quinol OH to the *si*- or *re*-face of the aldehyde. The formation of this new stereogenic center modifies the stereochemical outcome of the addition of a simple nucleophile to quinol **3**. As the result of creating 3 new stereogenic centers, the number of stereoisomers becomes 8 instead of 4 (in the simple case of addition of a nucleophile to **3**) which depends on the face selectivity in the approach to the aldehyde (*re* or *si* face) and the face selectivity in the approach to the enone (*re* or *si* face of the β-Carbon), as well as the doble bond selectivity (β-Carbon pro-*R* or pro-*S*) during the oxa-Michael addition. These three factors in the domino reaction of the synthesis of bicyclic dioxolanes result in four possible diastereoisomers with their two enantiomers each one (**Scheme 2.74**). Fortunately, only two of the four possible diastereoisomers were observed and, in accordance with the previously discussed structural determination, they are ***cis*-fused**.



Scheme 2.74

The possible stererochemical outcome of the process is indicated in **Scheme 2.75**. The initial 1,2-addition of the nucleophilic *p*-quinol oxygen to the *si*-face of the aldehyde generates the intermediate hemiacetal anion **I** with the *S* configuration at the newly generated stereogenic center. The oxa-Michael addition step could then occur on either of the two

prochiral β-carbons of the cyclohexadienone, from the face of the *p*-quinol containing the initial OH group, which is favored on steric grounds,[49] and leads to the *cis*-fused five-membered ring. As can be seen, the 1,4-intramolecular addition to the pro-*S* β-carbon (see intermediate **Ia**, **Scheme 2.75**) affords the major diastereoisomer **73** (2*S**, 3a*R**, 7a*S**) with the methyl and the aryl groups in a *cis* relative disposition in the 1,3-dioxolane ring. The attack to the pro-*R* β-carbon (intermediate **Ib**) explains the formation of the minor epimer (2*S**, 3a*R**, 7a*S**)-***epi*-73**. Intermediate **Ib** shows a destabilizing 1,3-parallel interaction between the C-aryl bond and the C_3-C_4 bond (bolded bonds), which is not present in **Ia**. The higher stability of the pro-*S* double bond attack, occurring through the transition state **Ia**, could explain the preferred formation of diastereomer **73** as the major one. A similar approach to the *re*-face of the aldehyde would give the same mixture of diastereomers with the opposite configurations. Thus, the initial OH attack to the *re*-face of the aldehyde generates the intermediate hemiacetal anion **II**. In this case, the intramolecular oxa-Michael addition to the pro-*R* β-carbon (intermediate **IIb**) gives access to the major dioxolane **73** (2*R**, 3a*S**, 7a*R**), which is the enantiomer of the major dioxolane resulting from the *si*-face addition on the aldehyde and the cyclization by the favored pro-*S* β-carbon. The attack to the pro-*S* β-carbon (intermediate **IIa**) is less favored due to the destabilizing 1,3-parallel interaction, appearing between the C-aryl bond and the C_3-C_4 bond (bolded bonds). This attack affords the minor diastereomer ***epi*-73** (2*R**, 3a*R**, 7aS***) which is the enantiomer of the derivative resulted in the *si*-face addition on the aldehyde followed by the oxa-Michael cyclation by the pro-*R* β-carbon.

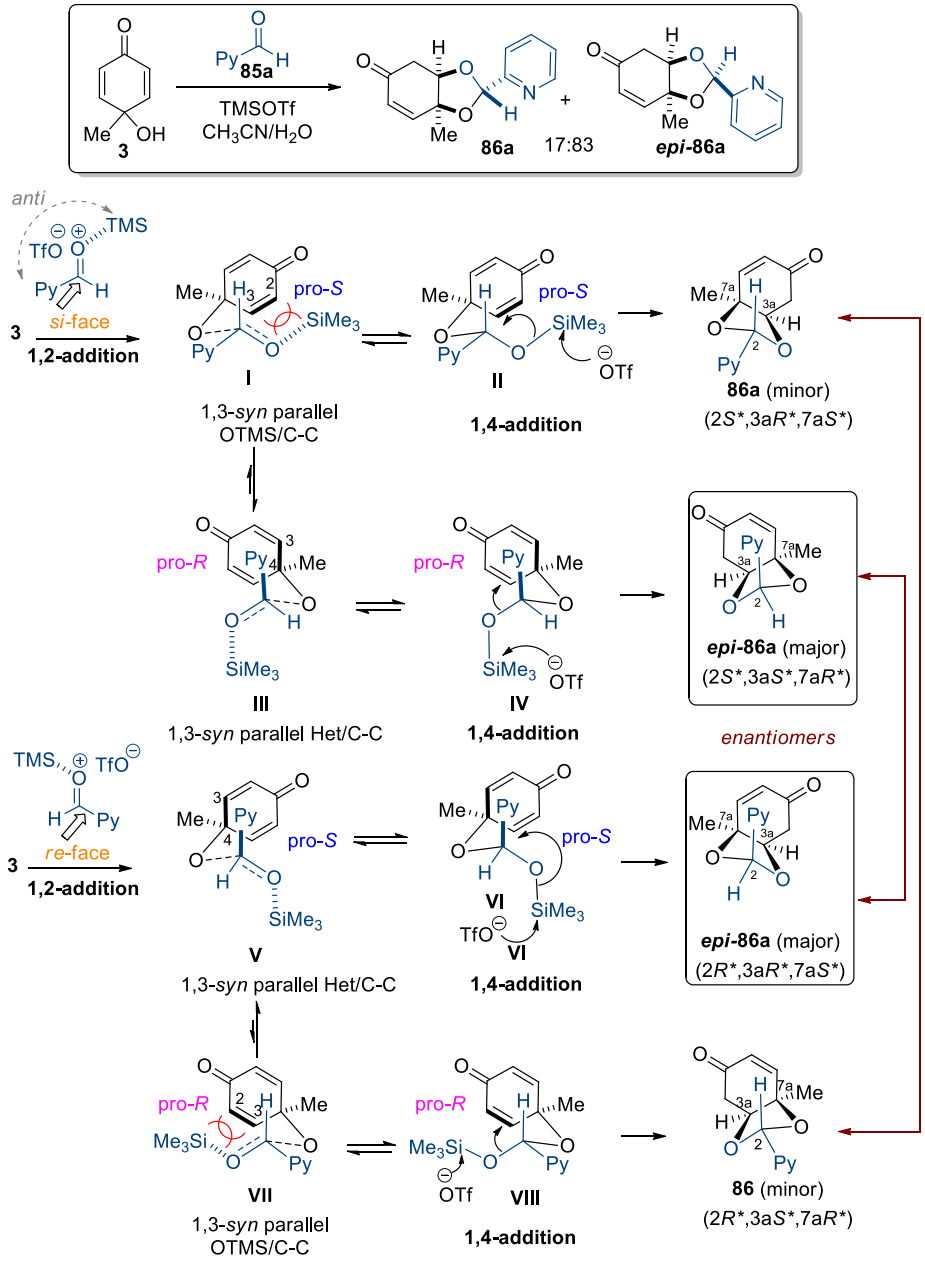


Scheme 2.75

The TMSOTf catalyzed reaction of **3** with pyridine-2-carboxaldehyde **85a**, gave a major diastereomer ***epi*-86a** having the heteroaromatic substituent *trans* with respect to the methyl group at C-7a. The mechanism and diastereoselectivity explaining these results are depicted in **Scheme 2.76**. The diastereoselectivity observed in this case, can be explained taking into account that the reactive species formed by association of TMSOTf (acting as a Lewis acid) to the heteroaromatic aldehyde must situate the TMS *anti* with respect to the heterocycle, to avoid steric interactions. The approach of the nucleophilic *p*-quinol OH to the *si*-face of this activated aldehyde can occur through orientations **I** and **III** represented in **Scheme 2.76**. When the *p*-quinol OH is approaching through species **I**, a destabilizing interaction between the bulky TMS group and the C_2=C_3 pro-*S* double bond of the cyclohexadienone moiety appears (intermediate **I**). Once the intermediate OTMS acetal **II** is formed, the 1,4-attack of the oxygen to the β-carbon of the pro-*S* double bond, promoted by the $TfO^{\ominus}$ would afford the minor diastereomer (2*S**,3a*R**,7a*S**)-***epi*-86a**. When the approach of the tertiary OH to the activated aldehyde takes place through the transition state **III**, the bulky TMS is situated far from the

pro-*R* double bond of the cyclohexadienone moiety. Although the transition species **III** and **IV**, leading to the major epimer ***epi*-86a**, show a 1,3-parallel interaction between the heteroaromatic group and the C_3-C_4 bond of the *p*-quinol (bolded bonds), this is the preferred evolution. Thus, the observed diastereoselectivity is suggesting that the interaction appearing in the initial attack to the aldehyde between the TMS-O bond and the C_2=C_3 pro-*S* double bond (intermediate **I**) is highly destabilizing and justifies the preferred evolution through species **III** with the subsequent 1,4-addition occurring on the pro-*R* β-carbon, where such interaction is not present, to give the major diastereomers (2*S**,3a*S**,7a*R**)-***epi*-86a**.

If we consider the attack of the nucleophilic *p*-quinol OH to the *re*-face of the TMSOTf activated heterearomatic aldehyde, represented as **V** and **VII** (**Scheme 2.76**), the bulky TMS is situated far from the cyclohexadienone moiety in the case of the approach to the pro-*S* double bond (transition state **V** and intermediate **VI**) affording the major diastereoisomer (2*R**,3a*R**,7a*S**)-***epi*-86a.** However, the highly destabilizing 1,3-parallel interaction between the TMS-O bond and the C_2=C_3 pro-*R* double bond appearing in the initial attack to the aldehyde in transition state **VII**, explains the minor formation of the minor diastereomer (2*R**,3a*S**,7a*R**)**-86a** after 1,4-addition of the acetal alkoxide **VIII** to the pro-*R* β-carbon.


85a
TMSOTf
CH3CN/H2O
3
86a 17:83 epi-86a
anti
si-face
1,2-addition
pro-S
pro-R
re-face
I
II
III
IV
V
VI
VII
VIII
1,3-syn parallel OTMS/C-C
1,3-syn parallel Het/C-C
1,4-addition
86a (minor)
(2S*,3aR*,7aS*)
epi-86a (major)
(2S*,3aS*,7aR*)
enantiomers
epi-86a (major)
(2R*,3aR*,7aS*)
86 (minor)
(2R*,3aS*,7aR*)

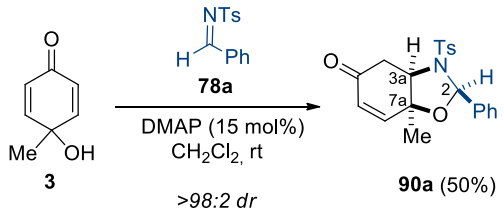
Scheme 2.76

2.2.3. Study of the base catalyzed reactions of p-quinols with imines.

Reactions of p-quinols with sulfonyl benzaldimines.

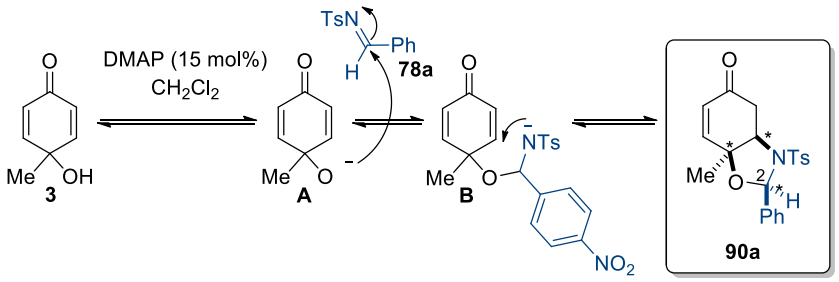
Having established the best reaction conditions (DMAP, CH_2Cl_2) allowing the synthesis of the *cis*-dihydrobenzo-[1,3]-dioxol-5(7aH)-ones derivatives from *p*-quinol and aromatic aldehydes, we decided to extend this study to aryl imines. The synthesis of amino functionalized *p*-quinol derivatives is of huge interest since the resulting multifunctional systems open the way to a variety of structures, not easily accessible in a direct manner. In spite of the potential interest of *p*-quinols, the reactivity between this ambident systems and imine derivatives had never been investigated.

We started our study screening the reaction conditions found to be optimal in the synthesis of *cis*-dihydrobenzo-[1,3]-dioxolanones from **3** and aldehydes. *N*-(*p*-tolylsulfonyl) benzaldimine **78a** was chosen as a model of electrophilic substrate, due to its stability and reactivity. The reaction between *p*-quinol **3** and **78a** in CH_2Cl_2, in the presence of 15 mol% of DMAP at room temperature, afforded the bicyclic hemiaminal ether **90a** as the only diastereomer detected in the crude reaction mixture, which could be isolated pure in 50% yield (**Scheme 2.77**). No aza MBH products were observed in the crude reaction mixture, although this process could have been taken place.



Scheme 2.77

This tetrahydrobenzo[*d*]oxazolone derivative must have been formed in an initial nucleophilic 1,2-addition of the hydroxy group of the *p*-quinol to the imine, facilitated by DMAP **(A)**, followed by an intramolecular aza-1,4-conjugated addition of the resulting hemiaminal intermediate to the cyclohexadienone **(B)** (**Scheme 2.78**).



Scheme 2.78

The structure of **90a** was confirmed by X-ray diffraction (**Figure 2.7**). As can be seen, the phenyl group at C-2 is situated in a *trans*-disposition with respect to both the C-7a methyl group and the H-3a, which in turn are *cis* to each other. This *trans* disposition is the inversed to that observed in the acid-catalyzed reactions of *p*-quinols with imines reported by Rovis.[21b] The stereochemical proposal explaining this result will be discuss in further sections.

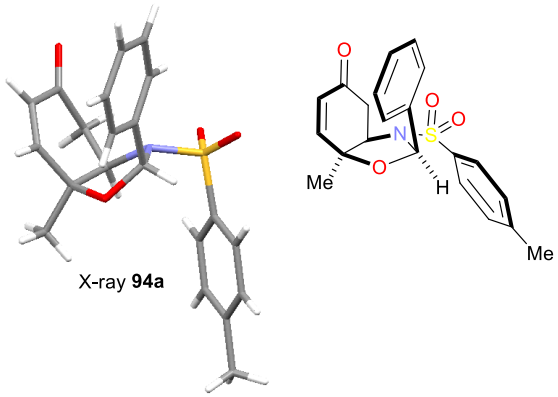
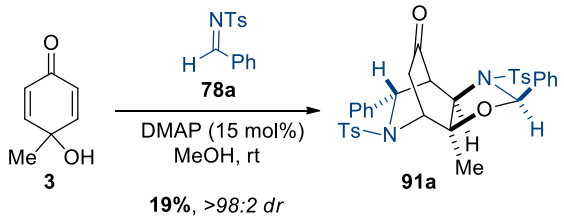


Figure 2.7

It is interesting to point out that the relative *trans* disposition of the aromatic C-2 substituent in the hydrobenzoxazolone derivative **90a** is the opposite to the one observed in the major diastereomers obtained in the synthesis of the analogues hydrobenzodioxolanones **73**, formed in the reaction of *p*-quinol **3** with aromatic aldehydes (see **Scheme 2.55** for X-ray of **73a**) . Therefore, the stereochemical outcome of the initial 1,2-addition of the hydroxy group of the *p*-quinol to the imines or aldehydes must have a substantial differentiation.

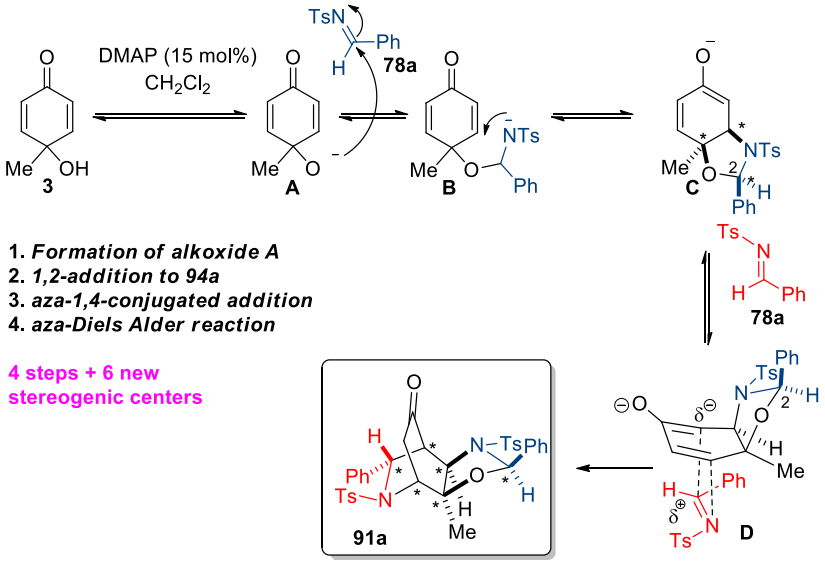
To our surprise, the reaction between *p*-quinol **3** and **78a** in MeOH, in the presence of 15 mol% of DMAP at room temperature, afforded the tricyclic structure **91a** as the only

diastereomer detected in the crude reaction mixture, which could be isolated pure in 19% yield (**Scheme 2.79**).



Scheme 2.79

This tricyclic derivative must have been formed in an initial nucleophilic 1,2-addition of the hydroxy group of the *p*-quinol to the imine, facilitated by DMAP **(A)**, followed by an intramolecular aza-1,4-conjugated addition of the resulting hemiaminal intermediate to the cyclohexadienone **(B)**. The resulting dienolate **C** must act as a diene with a second molecule of imine, acting as a heterodienophile to afford, through transition state **D**, **91a** in a domino process of 4 steps generating 6 new stereogenic centers in a controlled manner (**Scheme 2.80**).



Scheme 2.80

The structure of **91a** was confirmed by X-Ray diffraction (**Figure 2.8**). As can be seen, the phenyl group at C-2 is situated in a *trans*-disposition with respect to both the C-7a methyl group and the H-3a (the same case than in bicyclic **90a**) and the phenyl group at C-9 in a *cis* disposition with respect to the methyl group at C-7a and *trans* with respect to the phenyl at C-

2. The stereochemical proposal explaining the formation of this heterotricyclic derivative will be discussed in next section.

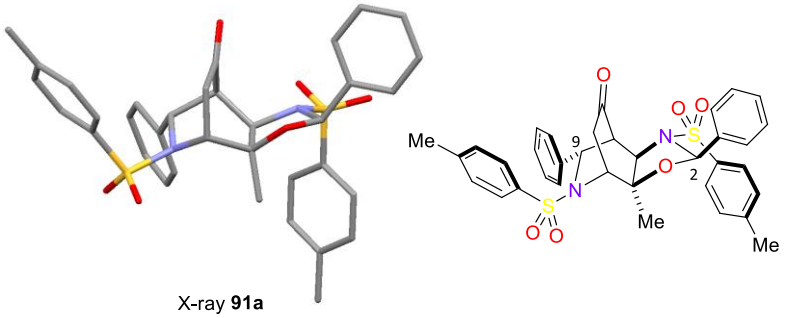
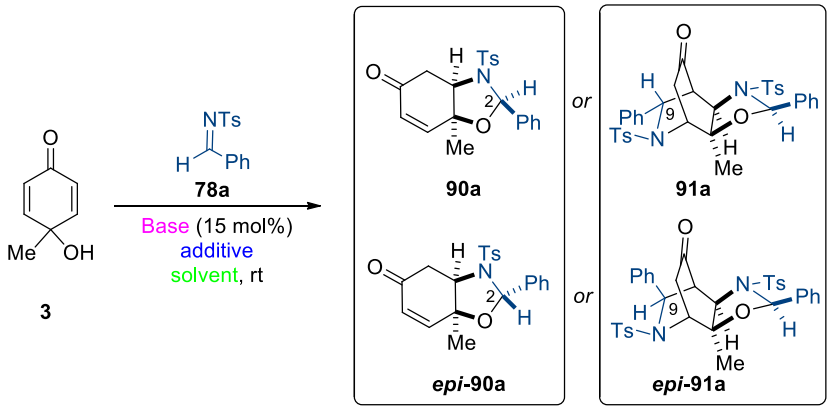


Figure 2.8

In order to check the influence of base, additives and solvents in the formation of bicyclic **90a** and its epimer ***epi*-90a** or tricyclic **91a** and other possible diastereoisomers, we decided to screen different conditions.

The results we obtained are summarized in **Table 2.7**. The results of the DMAP catalyzed reaction, in CH_2Cl_2 and MeOH already mentioned, were also included. The reaction of *p*-quinol **3** with *N*-*p*-toluenesulfonyl benzaldimine **78a** in DMAP and CH_2Cl_2 afforded bicyclic **90a** as the only diastereoisomer in 50% isolated yield (**Table 2.7, entry 1**)**.** The reaction using MeOH as solvent in the presence of DMAP allowed the formation of tricyclic **91a**, as the only diastereisomer observed in the crude reaction in 19% isolated yield (**Table 2.7, entry 2**). When $LiClO_4$ is added as an additive in 70 mol% to the DMAP catalyzed process in MeOH, only tricyclic derivative **91a** was formed with the same diastereoselectivity but in 50% yield (**Table 2.7, entry 3**). The influence of the additive in the reaction carried out in MeOH was thus significant. The DABCO (15 mol%)/$LiClO_4$ (70 mol%) catalyzed reactions were also effective in different solvents. Thus bicyclic oxazolones **90a** and its C-2 epimer ***epi*-90a** were obtained in a 90:10 ratio and 44% conversion using CH_2Cl_2 (**Table 2.7, entry 4**) and a similar conversion (42%) but a lower diastereoselectivity (70:30) was obtained when the solvent was MeOH (**Table 2.7, entry 5**). Surprisingly, the change to THF, afforded tricyclic compound **91a** as the only diastereomer in 50% isolated yield (**Table 2.7, entry 6**). In the absence of $LiClO_4$, a lower conversion is observed of the tricycle **91a** (**Table 2.7, entry 7**). Upon heating to 65 °C or irradiating in a Microwave oven (MW) a 95:5 mixture of inseparable **91a** and its epimer C-9 ***epi*-91a** resulted (**Table 2.7, entries 8 and 9 respectively**). The non-nucleophilic base Cs_2CO_3

could also promote the formation of the tricyclic derivatives **91a** and ***epi*-91a** in a lower diastereoselectivity using THF (63:37, 31% isolated yield) or MeOH (60:40, 40% isolated yield) as solvent (**Table 2.7, entries 10 and 11 respectively**).

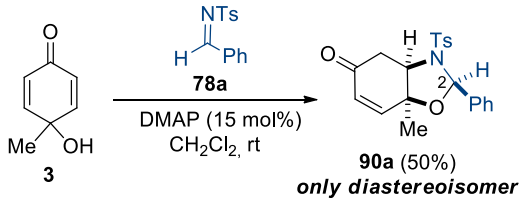


Entry	Base	Additive	Solvent	Yield (%)	Product (*d.r.*)[a]
1	DMAP	-	CH_2Cl_2	50	**90a**/***epi*-90a** (98:2)
2	DMAP	-	MeOH	19	**91a**/***epi*-91a** (98:2)
3	DMAP	$LiClO_4$ (70 mol%)	MeOH	50	**91a**/***epi*-91a** (98:2)
4	DABCO	$LiClO_4$ (70 mol%)	CH_2Cl_2	44[b]	**90a**/***epi*-90a** (90:10)
5	DABCO	$LiClO_4$ (70 mol%)	MeOH	42[b]	**90a**/***epi*-90a** (70:30)
6	DABCO	$LiClO_4$ (70 mol%)	THF	50	**91a**/***epi*-91a** (98:2)
7	DABCO	-	THF	20 (conversion)	**91a**/***epi*-91a** (98:2)
8	DABCO	$LiClO_4$ (70 mol%)	THF[c]	53	**91a**/***epi*-91a** (95:5)
9	DABCO	$LiClO_4$ (70 mol%)	THF[d]	53	**91a**/***epi*-91a** (95:5)
10	Cs_2CO_3	-	THF	31	**91a**/***epi*-91a** (67:37)
11	Cs_2CO_3	-	MeOH	40	**91a**/***epi*-91a** (60:40)

[a] Diastereomeric ratio measured by ^{1}H-NMR spectroscopy of the crude reaction; [b] Conversion calculated by ^{1}H-NMR spectroscopy of the crude reaction; [c] Temperature = 66°C; [d] Microwave irradiation

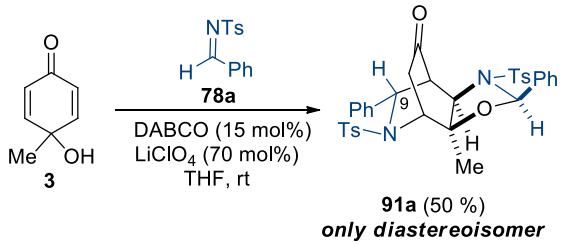
Table 2.7

As a summary of the results obtained it is important to remark that the first experimental conditions screened (DMAP (15 mol%) in CH_2Cl_2) gave the best yields and diastereoselectivity in the synthesis of bicyclic derivatives **90a** (**Scheme 2.81**).



Scheme 2.81

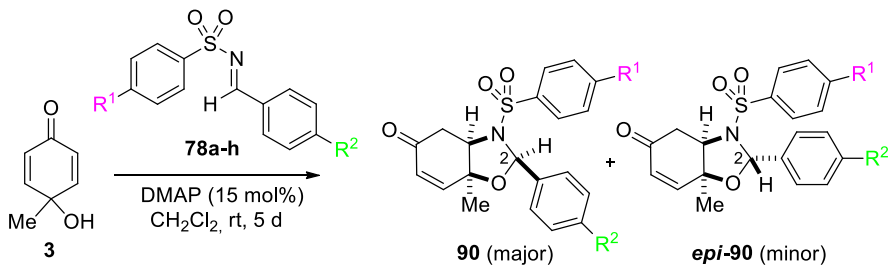
The DABCO/$LiClO_4$ catalyzed process in THF as solvent at room temperature was established as the best conditions to obtain tricyclic derivative **91a** (although the combination of DMAP/ $LiClO_4$ in MeOH also gave the same result) (**Scheme 2.82**).



Scheme 2.82

Scope of the reaction of *p*-quinol 3 with sulfonyl benzaldimines 78a-h. Synthesis of bicyclic derivatives 90/*epi*-90.

In order to evaluate the influence of substitution at the aromatic ring of the benzaldimine, as well as at the *N*-aryl sulfonyl group, in the synthesis of tetrahydrobenzo[*d*]oxazolone derivatives, we studied the reactions of *p*-quinol **3**, under the DMAP base catalyzed conditions, using differently substituted imines having both electron withdrawing and electron donating groups at the aromatic aldehyde precursor and at the aromatic ring of the sulfonamide (**Scheme 2.83**).



Scheme 2.83

The results are summarized in **Figure 2.9** where we have also included the above mentioned result. We initiated the study with *N*-aryl benzaldimines changing the substituent at the aryl sulfonyl group. When electron donating substituents were present in the sulfonyl benzaldimine **78a** (R^1 = Me, R^2 = H) and **78b** (R^1 = OMe, R^2 = H), good conversion and diastereoselectivities were achieved although the later was slightly worse. In the reaction of *p*-toluenesulfonylbenzaldimine **78a**, a 50% isolated yield of **90a** was obtained as the only diastereoisomer in the crude reaction whereas the reaction of *p*-quinol **3** with *N*-(4-methoxy) phenyl sulfonyl benzaldimine **78b** in DMAP/CH_2Cl_2 catalyzed system gave a diastereomeric ratio of 86:14 of **90b/*epi*-90b** with 68% isolated yield of the major diastereoisomer **90b**. Surprisingly, when the aromatic ring of the *N*-aryl sulfonyl moiety of the imine had an electron withdrawing (EWG) substituent **78c** (R^1 = NO_2, R^2 = H), the reaction proceeded with a low conversion (21%) after five days, to give a 86:14 mixture of N,O-acetals **90c** and ***epi*-90c** which could not be isolated. Characterization of ***epi*-90** was not an easy task since purification by column chromatography doesn't afford ***epi*-90**. Only ***epi*-90e** could be characterized unequivocally on the base of the ^{1}H-NMR spectrum of a 76:24 mixture of **90e/*epi*-90e**. Working with the *N*-*p*-tolylsulfonylimines (R^1 = Me), we could evaluate the behavior of imines having different substitution at the aromatic ring proceeding from the aldehyde. Imine **78d** with an electron donating substituent (R^2 = OMe) decreased significantly the conversion and stereoselectivity. Imine **78e** (R^2 = CF_3) led to the formation of a 76:24 mixture of **90e** and ***epi*-90e** in an almost complete process (conversion >98), obtaining 50% of isolated **90e**. Imines **78f** (R^2 = F), **78g** (R^2 = CN) and **78h** (R^2= NO_2) also evolved through an efficient process in a highly diastereoselective manner to give the N,O-acetals, thus evidencing that the presence of EWG at the imine moieties was favoring the formation of diastereomers **90f**, **90g** and **90h** which were isolated in 50%, 77% and 68% yield, respectively. This was expected since the electrophilic character of the iminic carbon is higher if EWG are present in the ring proceeding from the aldehyde precursor.

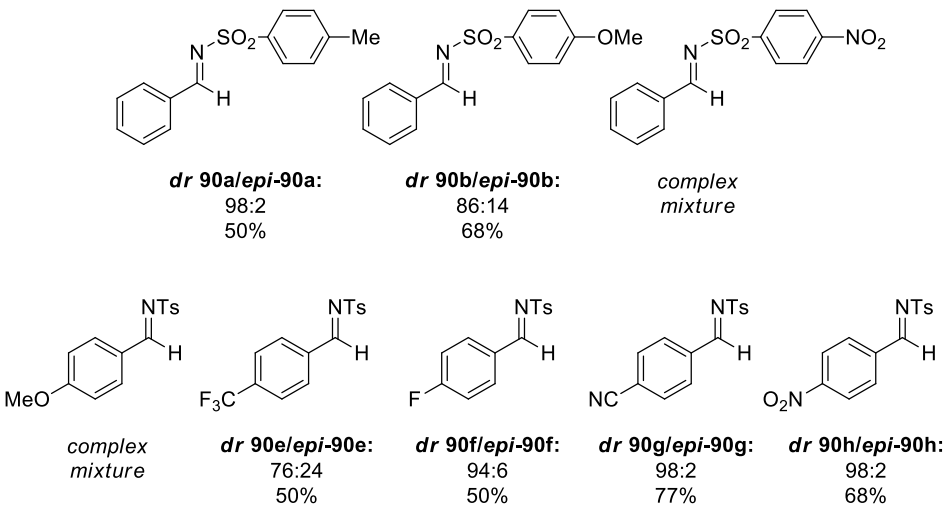
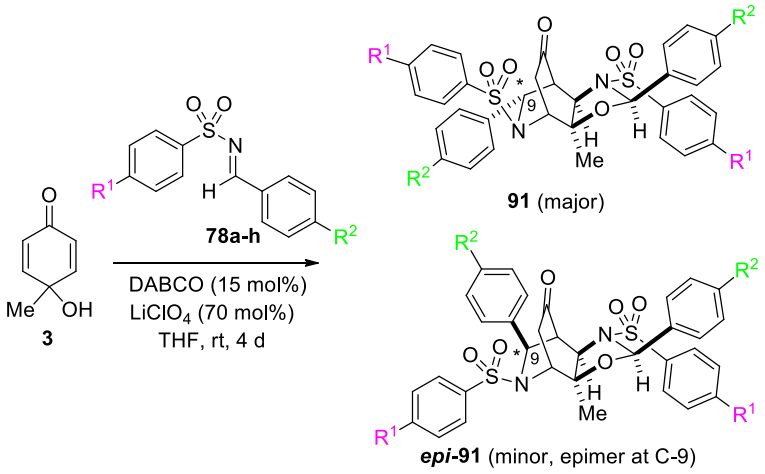


Figure 2.9

Scope of the reaction of *p*-quinol 3 with sulfonyl benzaldimines 78a-h. Synthesis of tricyclic derivatives 91/*epi*-91.

A parallel substrate scope study was carried out for the one-pot stereoselective formation of the heterotricyclic skeleton **91** observed when the reaction of *p*-quinol **3** with imines **78** was carried out in DABCO/$LiClO_4$ catalytic system, in THF at room temperature (**Scheme 2.84**).



Scheme 2.84

The diastereomeric ratios and isolated yields are summarized in **Figure 2.10**. When electron donor substituents were present in the aryl sulfonyl ring as in the case of **78a** (R^1 = Me, R^2 = H) and **78b** (R^1 = OMe, R^2 = H), excellent diastereoselectivities (>98 in both cases) and good yields of diastereomer **91** were achieved (50 and 80% isolated yield of **91a** and **91b** respectively). *N*-*p*-nitrophenylsulfonyl benzaldimine **78c** reacted with *p*-quinol **3** in the

presence of DABCO/$LiClO_4$ in THF at rt to give a diastereomeric mixture of tricyclic compounds **91c** and its C-9 epimer ***epi*-91c** in a 75:25 ratio and 48% yield. The influence of the substitution on the aromatic aldimine was studied using the *N*-tosyl aldimines (R^1 = Me) derived from *p*-methoxy, *p*-trifluoromethyl, *p*-fluor, *p*-cyano and *p*-nitro benzaldimines **78d**-**h**. The methoxy phenyl substituted *N*-tosyl aldimine **78d** (R^2 = OMe) afforded a 92:8 mixture of **91d** and ***epi*-91d**, as determined in the crude reaction mixture. The minor diastereoisomer, could not be isolated pure nor fully characterized. The *p*-CF_3 and *p*-F substituted benzaldimines **78e** and **78f** afforded mixtures of diastereomeric tricyclic compounds (85:15 and 90:10 respectively) from which only the major diastereomers **91e**, **91f** could be isolated pure (47% of **91e** and 40% of **91f**). Unfortunately, the *p*-cyano and *p*-nitro substituted benzaldimines **78g** and **78h** afforded complex reaction mixtures.

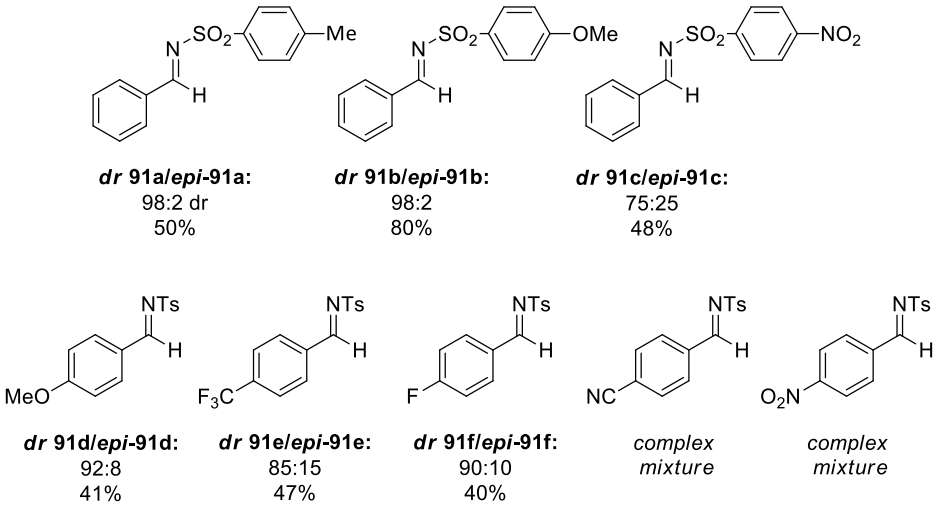
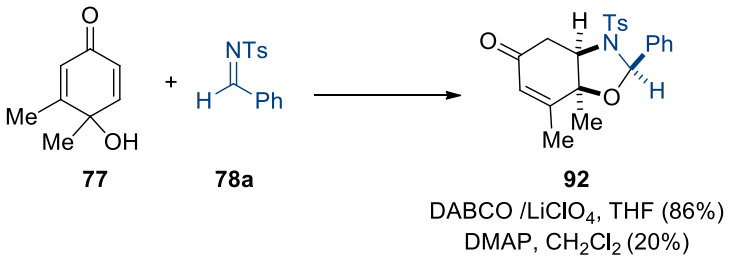


Figure 2.10

We finally checked the reaction of 3-methyl-4-hydroxy-4-methyl quinol **77** with *N*-tosylbenzaldimine **78a**, under the conditions previously established for the formation of both the heterobicyclic and tricyclic systems. Nonetheless, the bicyclic hemiaminal ether derivative **92** was isolated as a unique diastereomer in both cases. Thus, DABCO/$LiClO_4$, THF, room temperature conditions gave compound **92** in an 86% isolated yield, while the DMAP catalyzed process in CH_2Cl_2, afforded only a 20% yield of **92** (**Scheme 2.85**).



Scheme 2.85

Structural assignment of tetrahydrobenzo[d]oxazolone structures.

The structure and relative stereochemistry of all the tetrahydrobenzo[*d*]oxazolones **90** and **92** and their C-2 epimers, were established on the base of their spectroscopic parameters, mainly ^{1}H-NMR data and NOESY experiments. Moreover, the stereochemical assignment was also based on the comparison of their ^{1}H-NMR parameters with those of **90a**, whose structure had been unequivocally established by X-Ray (**Figure 2.11**). In the bicyclic oxazole, the methyl group at C-7a and the hydrogen at C-3a are in a relative *cis* disposition and the C-2 aryl substituent is in *trans* disposition, as it can be seen in the X-Ray structure of **90a** (**Figure 2.11**).

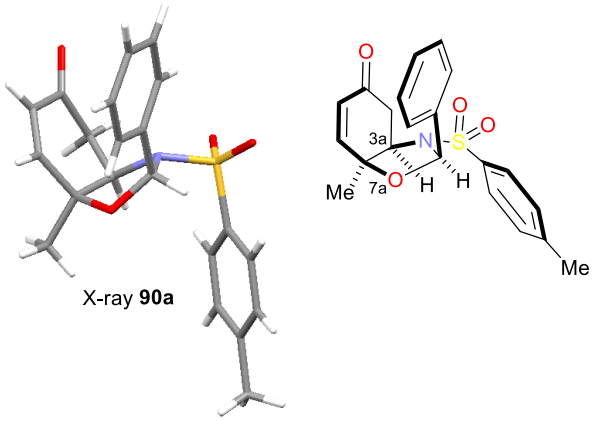


Figure 2.11

The relative configuration of the diastereoisomers N,O-acetals **90** and ***epi*-90** was established on the base of the following spectroscopic features observed in the ^{1}H-NMR spectra of **90e** and ***epi*-90e**.

Again, the existence of a characteristic *W*-type coupling constant between the olefinic hydrogen at C-7 and H-3a was observed in the minor diastereoisomer ***epi*-90e** as a consequence of the *cis* junction of the bicyclic system (**Figure 2.12**).

In the major of the tetrahydrobenzo[*d*]oxazolone **90e**, the *cis* ring fusion had been unequivocally established by X-Ray.

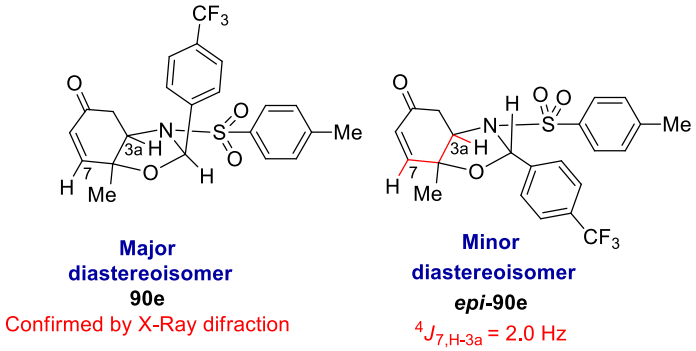


Figure 2.12

Another significant feature to confirm the different configuration at C-2 of N,O-acetals **90** and their epimers ***epi*-90** is the chemical shift of H-2 in both diastereomers. The ^{1}H NMR spectra evidenced a small but noticeable difference in the chemical shift of H-2 in both diastereomers. In the major one (**90e**) having the aryl substituent in the axial disposition, the equatorial H-2 appeared at lower field ($\delta_{H\text{-}2}$ = 6.14 ppm) than in the minor epimer ***epi*-90e** where the H-2, situated in the axial disposition, appeared at higher field ($\delta_{H\text{-}2}$ = 5.93 ppm) (**Figure 2.13**).

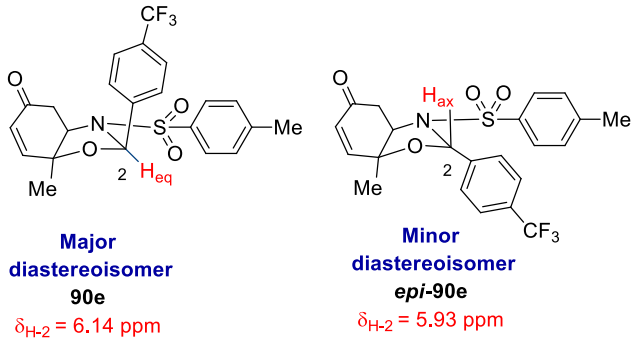


Figure 2.13

Finally, the stereochemistry of the minor epimers was also corroborated by bidimensional NOESY experiments for *epi*-90e. In this case, a NOE effect is observed between H-3a and the Me group at C-7a which confirms again the *cis*-fusion of the bicyclic system. No NOE effect between H-3a and H-2 was observed thus evidencing again the proposed stereochemistry (**Figure 2.14**).

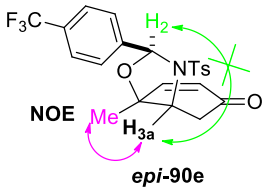


Figure 2.14

Structural assignment of tricyclic structures.

The tricyclic structure of **91** is of remarkable interest due to the presence of pyperidine and hydroxazole rings, which are common cores of natural products and biologically significant compounds (**Figure 2.15**).

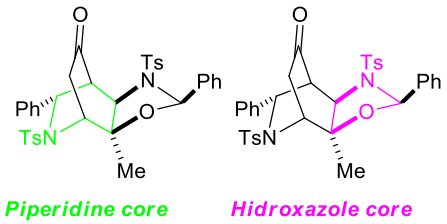


Figure 2.15

As can be seen in **Figure 2.16**, where the X-Ray diffraction structure of **91a** is shown, the phenyl group at C-2 is situated in a *trans*-disposition with respect to both the C-7a methyl group and the H-3a, which in turn are *cis* to each other (the same case than in the bicyclic **90a** structure). The phenyl group at C-9 is also in a *cis* disposition with respect to the methyl group at C-7a and *trans* with respect to the phenyl at C-2.

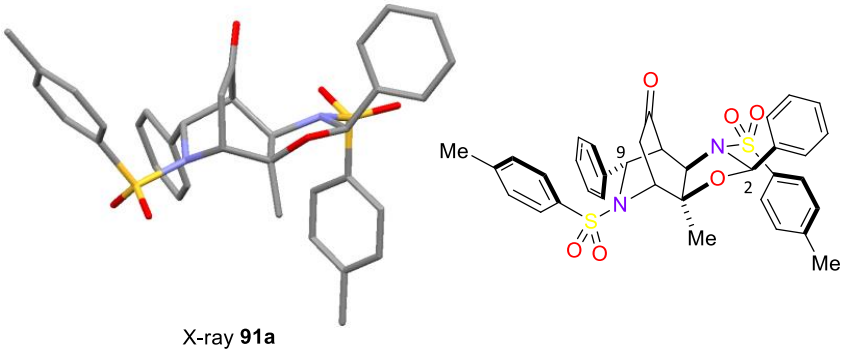


Figure 2.16

The assignment of the stereochemistry of the minor diastereomer ***epi*-91a** was achieved by bidimensional NOESY experiments. While in the case of the major epimer **91a** a NOE effect exists between **H-9** and one of the two hydrogens on C-6 (**H-6**), this NOE was no longer observed in the NOESY experiment of the minor epimer ***epi*-91a**. In fact, in the minor diastereoisomer ***epi*-91a**, a NOE effect between H-9 and the **Me** group at C-7a and also between **H-9** and **H-3a** could be observed (**Figure 2.17**). These relationships evidenced that the minor diastereoisomer observed in the synthesis of the tricyclic derivative must be the epimer at C-9.

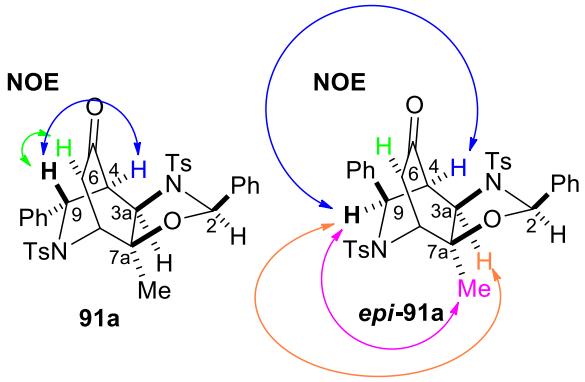


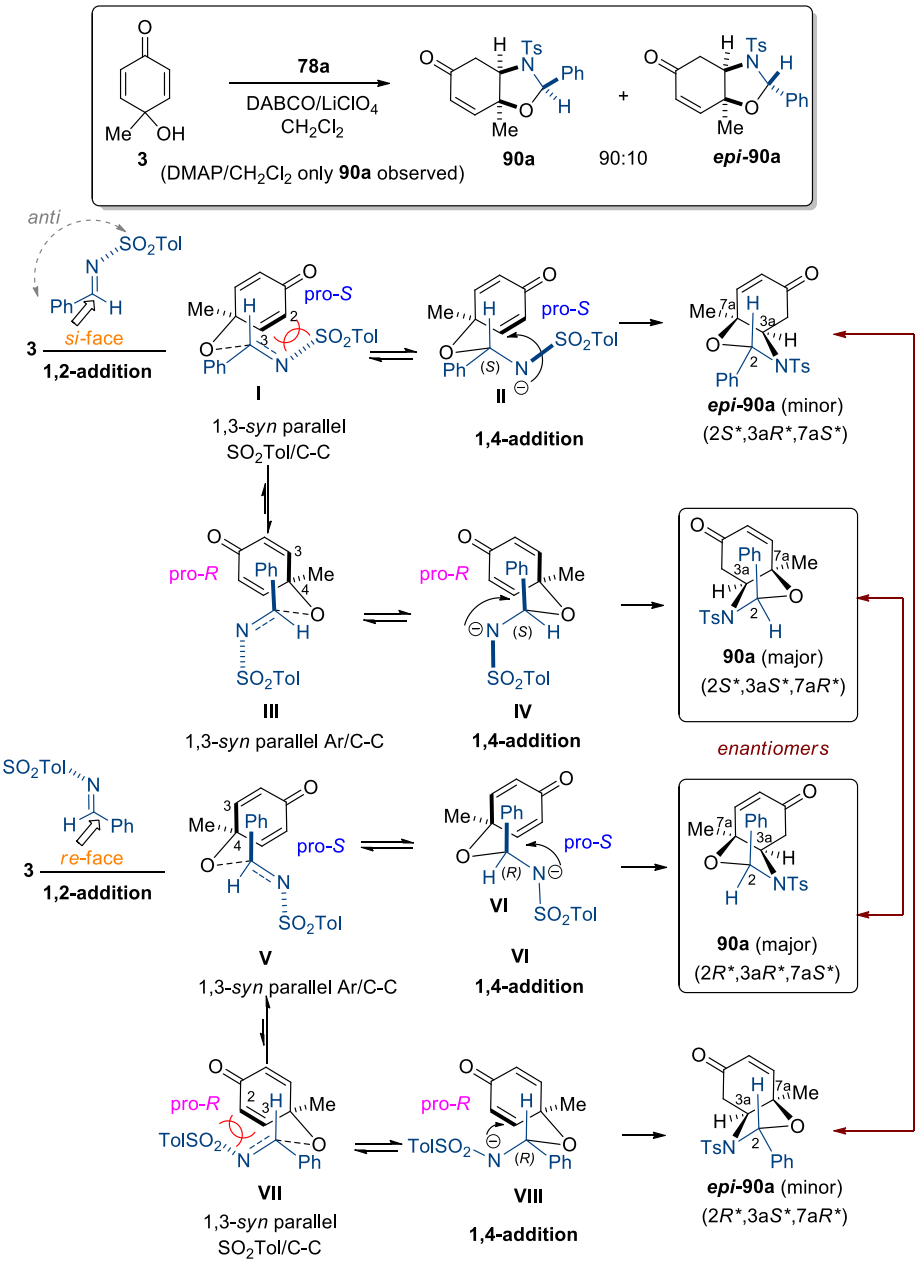
Figure 2.17

Mechanism and stereochemistry for the formation of tetrahydrobenzoxazolones and heterotricyclic derivatives.

The reactions of *p*-quinol **3** with aryl sulfonyl aldimines under DMAP catalyzed conditions in CH_2Cl_2, led to the formation of tetrahydrobenzoxazolone structures, having a *cis* relative fusion of the five and six membered rings and a *trans* disposition of the aryl group situated at C-2 with respect to Me at C-7a (in the case of major epimer **90a**). In the case of the reaction of *p*-quinol **3** with *N*-tosylarylimines under DABCO/$LiClO_4$ catalyzed conditions and using CH_2Cl_2 as solvent, two diastereoisomers are observed. The reactive *N*-tosylarylimine must situate the tosyl group *anti* with respect to the aromatic group, to avoid steric interactions. The initial deprotonation of *p*-quinol **3** by DABCO gives a *p*-quinol alkoxide whose approach to the aldimine **78a**, can take place from the *si*-face or the *re*-face. As shown in **Scheme 2.86**, the attack to the *si*-face of the *anti p*-tolylsulfonyl benzaldimine **78a**, oriented to the pro-*S* double bond of the cyclohexadienone, gives species **I**, with the bulky SO_2Tol group developing a highly destabilizing 1,3-parallel interaction with the C_2=C_3 double bond of the cyclohexadienone moiety. The evolution through the aza-Michael addition to the pro-*S* β-carbon, represented as species **II**, could explain the formation of the diastereomer (2*S**, 3a*R**, 7a*S**)-***epi*-90a** as a minor diastereoisomer due to the destabilizing interaction which emerges in **II**. The results are suggesting that interactions due to the 1,3-parallel disposition of the Ph and the C_3-C_4 bond emerging in species **III** and **IV**, when the nucleophilic nitrogen is approaching to the pro-*R* double bond, is less energetically demanding than those arising when the SO_2Tol group and the C_2=C_3 double bond are 1,3-parallel as in **I** and **II**. Thus, the aza-1,4-conjugated addition to the pro-*R* β-carbon through species **IV** must be favored explaining the formation of the major diastereoisomer (2*S**, 3a*S**, 7a*R**)-**90a** (**Scheme 2.86**).

The attack of the OH of the *p*-quinol through the *re*-face of the anti sulfonyl imine oriented to the pro-*S* double bond, represented as **V**, is situating the bulky SO_2Tol group far from the cyclohexadienone moiety. Although a 1,3-parallel interaction between the Ph and the C_3-C_4 bond of the 2,5-cyclohexadienone moiety appears in **V**(bolded bond), this 1,4-approach must be favored over the pro-*S* double bond because the bulkiest tosyl group is far from any other group. Once the O-C-N bond is formed, an aza-Michael attack of the negative nitrogen to the pro-*S* β-carbon, represented as **VI,** explains the formation of the major diastereomer (2*R**, 3a*R**, 7a*S**)-**90a**.

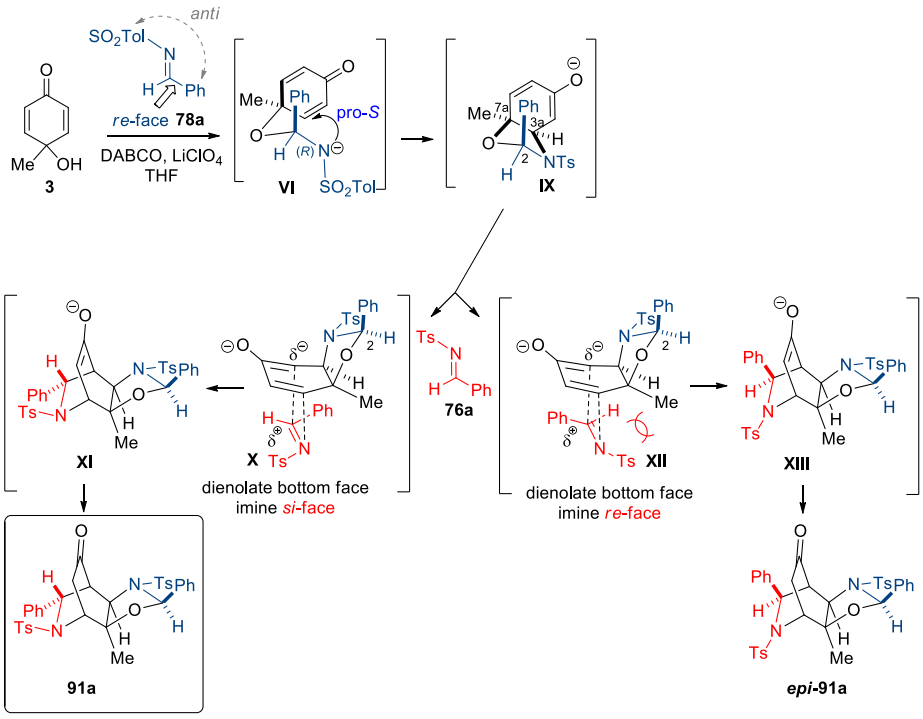
However, the *re*-face attack oriented to the pro-*R* double bond presents the destabilizing 1,3-parallel interaction between the SO_2Tol group and the C_2=C_3 double bond (see intermediate **VII**) which explains the formation of the minor diastereoisomer (2*R**, 3a*S**,***epi*-90a**. Both the approach of the tertiary *p*-quinol OH to the *si*-face of the anti sulfonyl imine followed by aza-Michael addition to the pro-*R* double bond through species **IV**, and the OH approach to the *re*-face of the imine followed by the aza-Michael addition to the pro-*S* double bond, through species **VI** are favored, leading to the formation of both enantiomers of the major diastereoisomer.



Scheme 2.86

When the reaction between *p*-quinol **3** and *N*-*p*-tolylsulfonyl benzaldimine **78a** was effected with Cs_2CO_3 using MeOH as solvent, the tricyclic compound **91a/*epi*-91a** was formed in a 60:40 ratio. Taking into account that the relative configuration of the stereogenic centers of the hydrobenzoxazolone moiety of **90a** is the same as in compound **91a** (phenyl and methyl substituents *trans*), we can assume that the first steps of the domino sequence are common. Thus, compound **91a** must result from a sequential process starting from deprotonation of the *p*-quinol **3** and addition to the *re*-face of the anti imine (**Scheme 2.87**, species **VI**) followed by the aza-Michael addition to the pro-*S* β-carbon of the cyclohexadienone moiety (species **IX**) (the attack to the *si* face of the imine and the corresponding aza-Michael addition to the pro-*R* β-carbon would give the enantiomer, thus the same result). The final tricyclic compound **91a** could be formed from the dienolate intermediate **IX** by a regio- and diastereoselective aza Diels-Alder reaction[64] with a second equivalent of the imine **78a**. The diastereoselectivity observed could be explained through the transition state represented as **X** in **Scheme 2.87**, where the *anti*-sulfonyl imine is approaching to the less hindered bottom face of the dienolate. Minimizing steric interactions are responsible of the favored attack of the imine, acting as heterodienophile, by its *si*-face. This approach leads to intermediate **XI** with the (*S*) configuration at the new stereogenic phenyl substituted carbon. Final enolate protonation afforded the observed diastereomer **91a.** The formation of the minor diastereoisomer must result from the transition state represented as **XII** (**Scheme 2.87**) where the attack of the enolate to the imine occurs by the *re*-face affording species **XIII**. After protonation of the enolate, to minor epimer ***epi*-91a** with *(R)* configuration at C-9 is formed. The transition state **XII**, must be less stable dure to the highly destabilizing interaction between the tosyl group and the methyl substituent, which is not present in transition state **X**.

[64] Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. in *Diels-Alder Reactions of Imino Dienophiles*, Organic Reactions, Vol. 65. pp 141-599, John Wiley & Sons, **2005**.



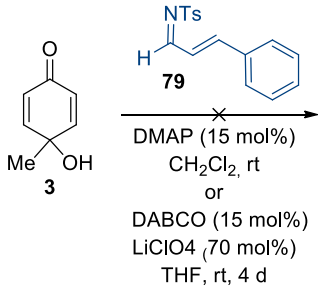
Scheme 2.87

Although a concertated aza-DA process has been proposed, a stepwise sequence of a 1,2-dienolate addition of **IX** to second imine **78a**, followed by a new aza-Michael addition to the cyclohexenone fragment could not be disregarded.

Reactions of p-quinols with other imines and ketimines.

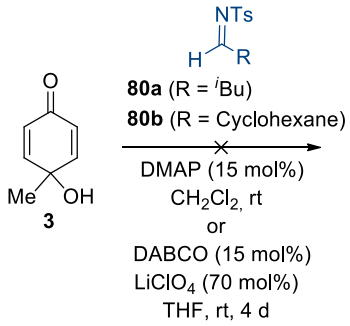
Reactions of *p*-quinols with α,β-unsaturated sulfonyl imines and aliphatic sulfonyl imines.

α,β-Unsaturated *p*-tolyl sulfonyl imine **79** was also used as electrophile in the DMAP and DABCO/$LiClO_4$ catalyzed reactions with *p*-quinol **3** in CH_2Cl_2 and THF respectively. Unfortunately, the starting materials were always recovered unaltered after 4 days (**Scheme 2.88**).



Scheme 2.88

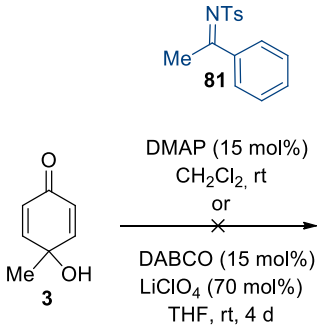
Aliphatic tosyl aldimines derived from butyraldehyde and cyclohexane carboxaldehyde **80a-b**, were also used as electrophiles in the DMAP and DABCO/$LiClO_4$ catalyzed reaction with *p*-quinol **3** in CH_2Cl_2 and THF respectively. Their poor reactivity did not allow reaching significant conclusions (**Scheme 2.89**



Scheme 2.89

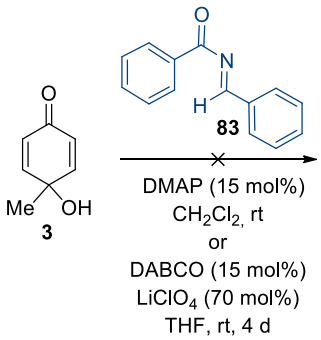
Reactions of *p*-quinols with sulfonyl ketamines and *N*-acyl benzaldimine.

The reaction with sulfonyl ketimine **81** did not afford any product. Thus, the starting materials were recovered unchanged (**Scheme 2.90**). This lack of reactivity could be due to the lower electrophilicity of the carbonylic carbon due to the inductive effect of the methyl group and to the steric hindrance around the imine carbon, which difficults the attack.



Scheme 2.90

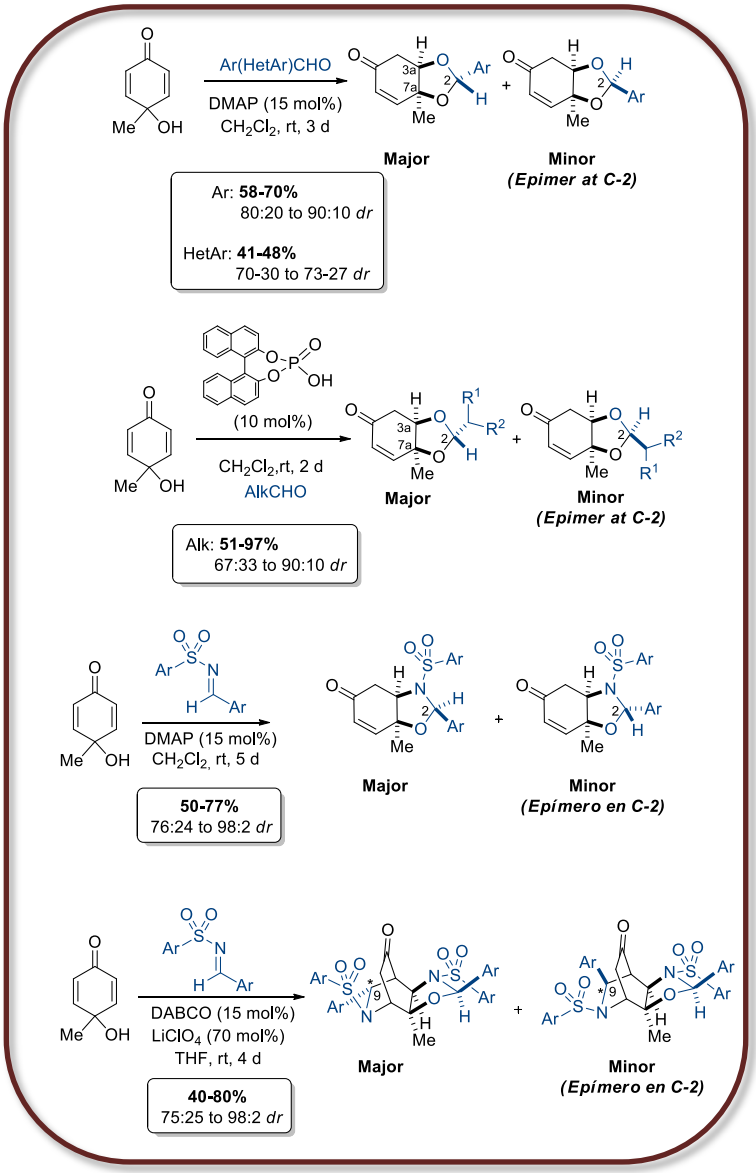
The reaction with N-benzoyl protected benzaldimine **83** afforded the starting materials unaltered either all the experimental conditions tried (**Scheme 2.91**).



Scheme 2.91

Study of base catalyzed reactions of *p*-quinols with aldehydes and imines:

As a summary of Chapter 2, in **Scheme 2.92** are shown the most important results obtained in the reactions of *p*-quinols with aldehydes and imines.



Scheme 2.92

Chapter 3

Study of Friedel-Crafts reactions of different heteroaromatic derivatives with p-quinols

3. Study of Friedel-Crafts reactions of different heteroaromatic derivatives with *p*-quinols.

3.1. Introduction and objectives.

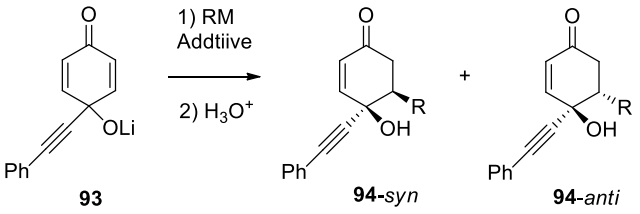
3.1.1. General aspects of the carbon nucleophiles conjugate additions to p-quinols.

The precedents of the conjugate addition of carbon nucleophiles to *p*-quinols have been classified in two main groups based on the type of stereoselective induction: organometallic and transition metal-catalyzed 1,4-addition reactions and organocatalytic reactions.[17] In both diastereoselective and enantioselective conjugate addition will be consider.

Organometallic and transition metal-catalyzed reactions.

Conjugate addition of organometallic reagents.

In 1988, Liotta[65] *et al.* developed the diastereoselective addition of Grignard or organocooper reagents over the lithium alcoxide of *p*-quinol **93**. They proposed that the alcoxide group controlled the diatereoselective course of the reaction giving the *syn* addition of the nucleophile by the same face of the alcoxide affording **94**-*syn* in good yield and excellent diastereoselectivity syn/anti (**Table 3.1, entries 1 and 2**).



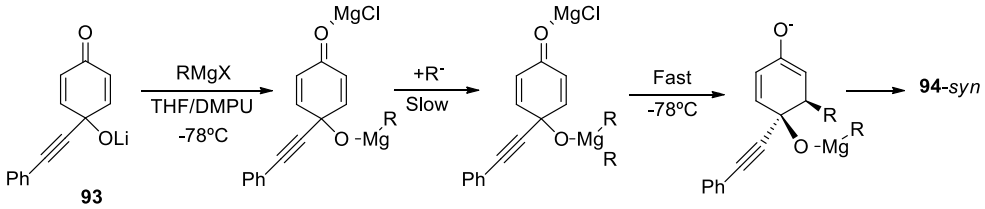
93 **94**-*syn* **94**-*anti*

Entry	RM	Additive	Yield (%)	*syn/anti*
1	BuMgCl	DMPU	83	100:0
2	EtMgBr	DMPU	86	100:0
3	$Li_2(Bu)_2CuCCN$	-	85	7:93

Table 3.1

[65] Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127.

This study was developed with 4-alkynyl substituted *p*-quinol **93** with the objective of minimize the sterical difference between the two faces of the enonic system and reinforce a face selection based on electronic effects. The *syn*-diastereoselectivity was explained by the *Ligand Assisted Nucleophilic Addition*[66] (LANA) mechanism. The alcoxide acts as an internal ligand which associates to the nucleophile which, in an intramolecular way, attacks to the electrophilic C-3 center of the molecule to mainly origin the conjugated addition product with *syn* stereochemistry with respect to the hydroxyl group. The use of DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) facilitates the transmetallation step favoring the stabilization of the lithium cation by coordination (**Scheme 3.1**).

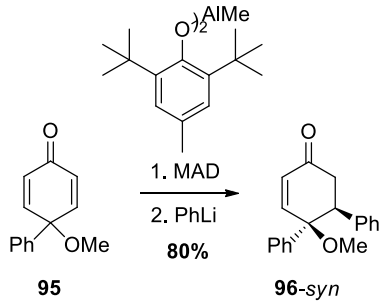


Scheme 3.1

The use of organometallic reagents with a full coordination sphere as the organocuprates gave the **94**-*anti* product with respect to the hydroxyl group (**Table 3.1, entry 3**). In this case, the association of the alcoxide to the nucleophile is not possible and the hydroxyl group cannot lead the attack.

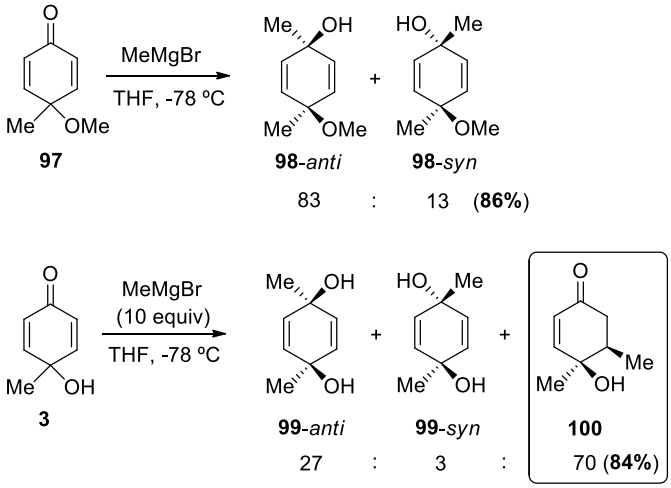
Swenton[67] *et al.*, have studied the diastereoselective conjugated addition of organolithium and Grignard reagents to *p*-quinols **95** with the hydroxyl group derived as methyl ether. All the reactions were performed by previous treatment of quinol **95** with MAD (methylaluminum bis*(*2,6-di-*tert*-butyl-4-methylphenoxide), a sterical hindered reagent used to complex carbonyl groups, and avoid the 1,2-addition reactions (**Scheme 3.2**). The results in the reaction with Grignard reagents and organolithium reagents showed that the methoxy group also acts as a tether and favor the attack of the organometallic reagent by its same face affording the conjugated addition products **96**-*syn*.

[66] (a) Solomon, M.; Jaminson, C. L.; McCormick, M.; Liotta, D. *J. Am. Chem. Soc.* **1988**, *110*, 3702; (b) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc*. **1990**, *112*, 9393.
[67] Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413.



Scheme 3.2

The group of Wipf[68] developed the diastereoslective 1,4-addition of organolithium or Grignard reagents to cyclohexadienones-4-alcoxy (**97**) or 4-hydroxy-4-alkyl substituted (**3**). This study showed that the addition of Grignard reagents and organolithium reagents over O-methyl or O-TMS *p*-quinols gave the 1,2-addition product **98** with the *anti*-approaching of the organometallic reagent with respect to the C-O bond at C-4 (**Scheme 3.3**).



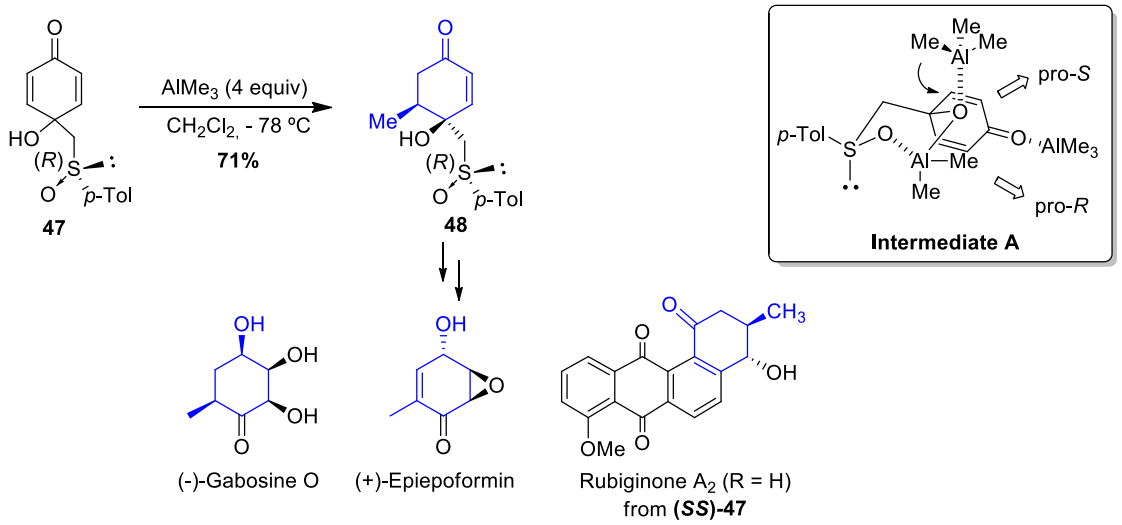
Scheme 3.3

As it was expected according to Liotta's results, when the addition was performed over the OH free *p*-quinol **3**, the major product was the conjugated addition product **100**, as the result of the *syn* directed addition by the alcoxide (**Scheme 3.3**).

As it was mentioned in Chapter 2, in 1995, our research group reported the synthesis of enantiopure 4-[*p*-(tolylsulfinyl)methyl]-*p*-quinol **47** and its reactivity in Diels-Alder reactions.[48] Shortly thereafter, our group described the diastereoselective addition of

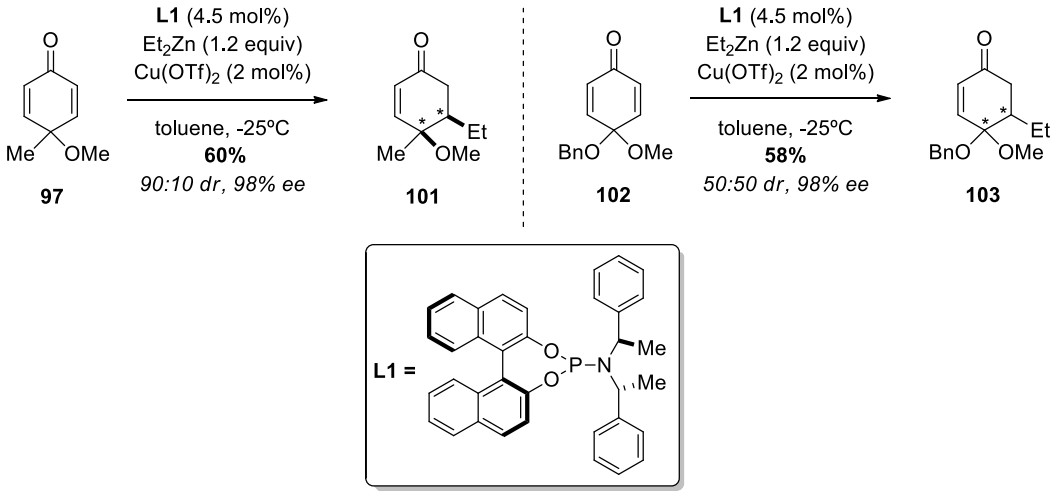
[68] Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *16*, 11678.

organoalanes (AlR_3) into the enantiopure sulfinymethyl-*p*-quinols **47** (**Scheme 3.4**).[23] In all cases, conjugate addition product, such as **48** was isolated as a single diastereomer. A highly organized transition state similar to **intermediate A** was proposed in order to explain the observed diastereoselectivity. Our research group has used this methodology numerous times in the enantioselective synthesis of different natural products such the (-)-Gabosine O,[27c] the (+)-Epiepoformin[27a] or Rubiginone A_2.[27b]



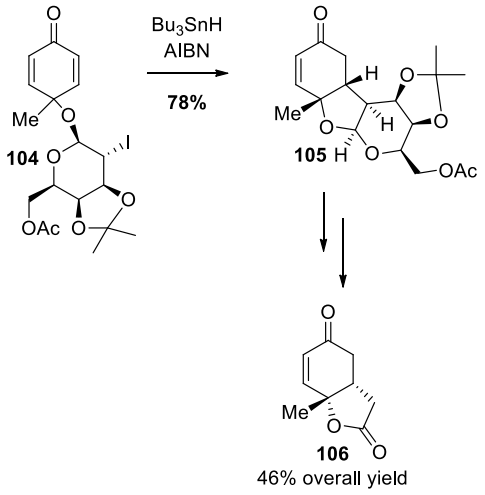
Scheme 3.4

In 1999, Feringa *et al.*[22] performed a series of studies on the cooper catalyzed conjugate addition of alkylzinc reagents in the presence of enantiopure phosphoramidites ligands **L1** (**Scheme 3.5**). The conjugate additions of Et_2Zn to substrate **97** provided the conjugate addition product **101** in high enantioselectivity and diastereoselectiviy. In order to explain that the diastereoselectivity of the reaction depends on the directing effect of the alcoxi substituent at C-4 they compare the result obtained with monoalkoxide **97** with that obtained with mixed dialkoxide **102**. In this case, product **103** was obtained as a 1:1 mixture of diastereomers. The authors explained that the observed diastereoselectivity might be due to either steric effects or coordination of the alkoxy group to the metal catalyst as it had been previously speculated.



Scheme 3.5

In 2010, Clive's group[69] developed a diastereoselective intramolecular radical cyclization of the chiral iodo-glycal substituted *p*-quinol **104** for the preparation of optically pure γ-lactones **106**. Reaction of the iodoether **104** with Bu_3SnH underwent a stannane-mediated radical cyclization. After acid hydrolysis of **105**, cleavage of the resultant diol followed by the decarboxylation, under Jones oxidation conditions, lactone **106** was obtained in 46% yield (**Scheme 3.6**).

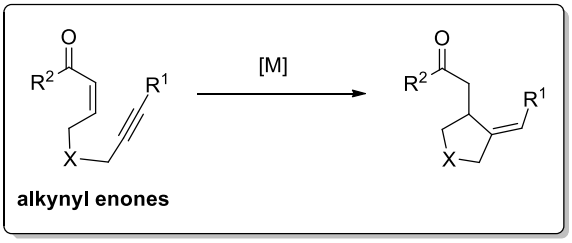


Scheme 3.6

[69] Sunasee, R.; Clive, D. L. J. *Chem. Comm.* **2010**, *46*, 701.

Enyne cyclizations.

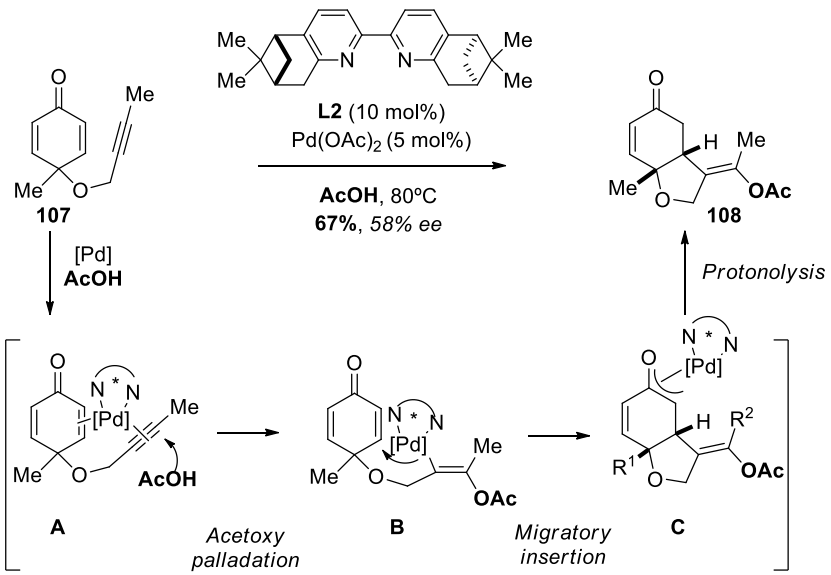
Metal-catalyzed cascade reactions are among the most important methods for assembling complex polycyclic molecules from simple polyunsaturated precursors. One of these examples is the cyclization of alkynyl enones initiated by transition metal catalysts such as Ni,[70] Pd,[71] or Rh[72] (**Scheme 3.7**).



Scheme 3.7

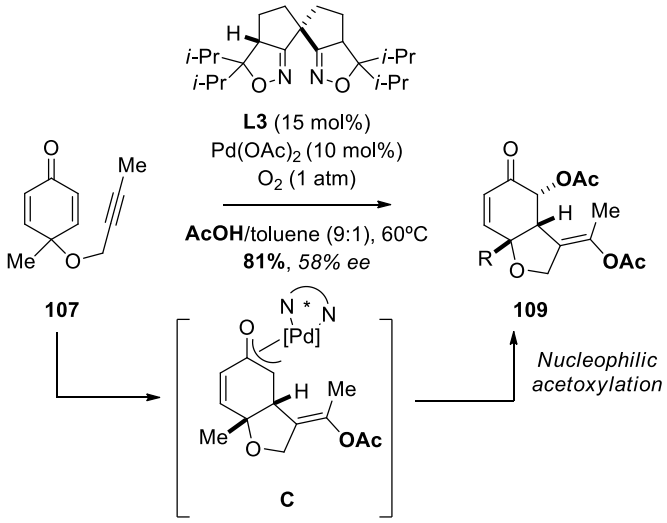
With the aim of synthetize polycyclic structures derived from *p*-quinol systems a variety of enantioselective enyne cyclizations of cyclohexadienones have been reported. Harned[73] *et al.* in 2013 reported a enantioselective Pd-catalyzed regioselective acetoxylation-cyclization sequence of alkyne-tethered cyclohexadienones **107** providing bicyclic enones **108** with moderate selectivity in the presence of chiral pinene-derived bipyridine **L2** (**Scheme 3.8**). This cyclization reaction is initiated by binding of the alkyne to the Pd(II) catalyst (**Intermediate A**). This binding will make the alkyne more electrophilic and allow the acetic acid to attack to the more electrophilic distal alkyne carbon through an anti-approaching, affording vinyl Pd **intermediate B**. Subsequent migratory insertion of the chiral organo palladium **intermediate B** is preferred on one of the prochiral conjugate positions. After protonation of resulting enolate **intermediate C** product **108** was obtained.

[70] Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc*. **1996**, *118*, 2099.
[71] Tsukamoto, H.; Suzuki, T.; Uchiyama, T.; Kondo, Y. *Tet. Lett.* **2008**, *49*, 4174.
[72] Ziyanak, F.; Kuş, M.; Artok, L. *Adv. Synth. Cat.* **2011***, 6*, 897.
[73] Tello-Aburto, R.; Kalstabakken, K. A.; Harned, A. M. *Org. Biomol. Chem*. **2013**, *11*, 5596.



Scheme 3.8

Sasai's group[74] recently reported a similar tandem cyclization process with the *O*-propargyl *p*-quinol **107** using $Pd(OAc)_2$, SPRIX (spiro-bis(isoxazoline)) **L3**[75] as the chiral ligand and O_2 (1 atm). Compound **109** was obtained in good yields and 58% *ee* (**Scheme 3.9**). In this case, the initially formed Pd enolate **intermediate C** appears to be long-lived enough to undergo a subsequent oxidation reaction by addition of AcOH to the enolate, which leads to the installation of the second acetate moiety (**Scheme 3.9**).

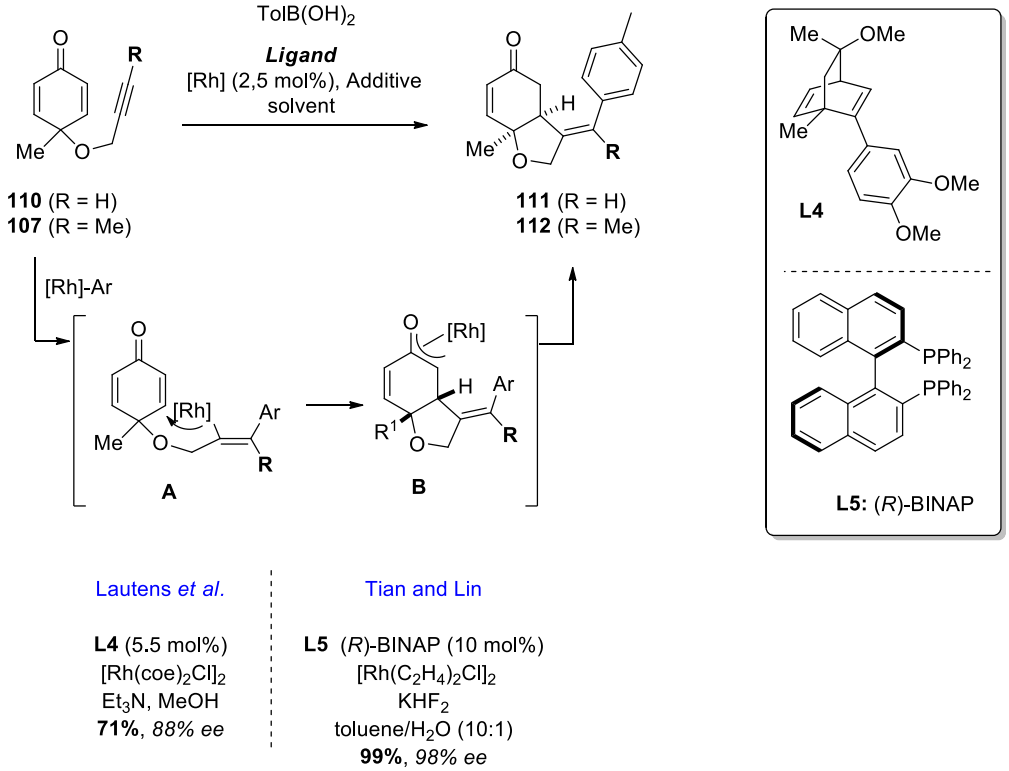


Scheme 3.9

[74] Takenaka, K.; Mohanta, S. C.; Sasai, H. *Angew. Chem. Int. Ed*. **2014**, *53*, 4675.
[75] Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett*. **1999**, *1*, 1795.

In 2013, Lautens and co-workers reported a Rh-catalyzed cyclization of terminal propargyl *p*-quinol ethers **110**.[76] As an illustrative example, *p*-quinol **110** and *p*-toluene boronic acid were treated with a catalytic amount of $[Rh(coe)_2Cl]_2$ in the presence of chiral diene ligand **L4** to afford bicyclic enone **111** in moderate yield and enantioselectivity (**Scheme 3.10**). The formation of **111** could be explained by the *syn*-addition of the [Rh]-Ar complex onto the alkyne framework of **110**, generating **intermediate A**, which upon cyclization, generated the Rh enolate **intermediate B**, that after hydrolysis gave the five-membered ring with the *exo*-cyclic double bond in a 71% yield and 88% *ee*.

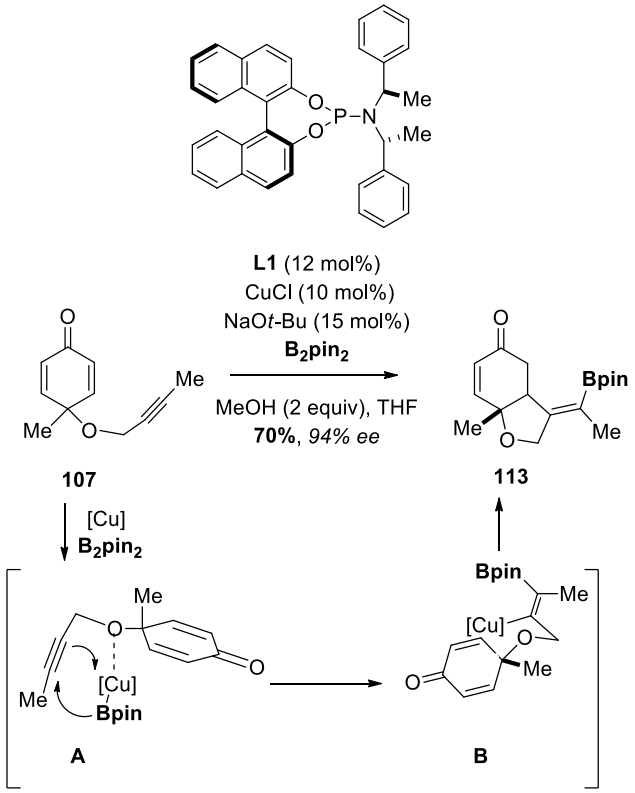
Tian and Lin[77] have published a similar Rh-catalyzed arylative cyclization in this case of substituted alkynes **107** using a catalytic amount of $[Rh(C_2H_4)_2Cl]_2$ with **L5** (*R*)-BINAP as the chiral ligand affording the hydrobenzofuran **112** in excellent yield (99%) and enantioselectivity (98% *ee*) (**Scheme 3.10**).



Scheme 3.10

[76] Keilitz, J.; Newman, S. G.; Lautens, M. *Org. Lett*. **2013**, *15*, 1148.
[77] He, Z.-T.; Tian, B.; Fukui, Y.; Tong, X.; Tian, P.; Lin, G.-Q. *Angew. Chem. Int. Ed*. **2013**, *52*, 5314.

Tian and Lin[78] have also reported a Cu-catalyzed borylative cyclization that provides the boron bicyclic enone **113** in good yield and a 94% *ee* using phosphoramidite **L1** as ligand (**Scheme 3.11**). The authors proposed a β-borylation of the alkyne **107**, mediated by an *O*-coordination of the propargyl ether unit of the cooper-boron **intermediate A**. The resulting borylated alkenyl-copper **intermediate B** could immediately undergo enantioselective conjugate addition to the cyclohexadienone moiety in a *syn* fashion to generate the chiral product **113**.



Scheme 3.11

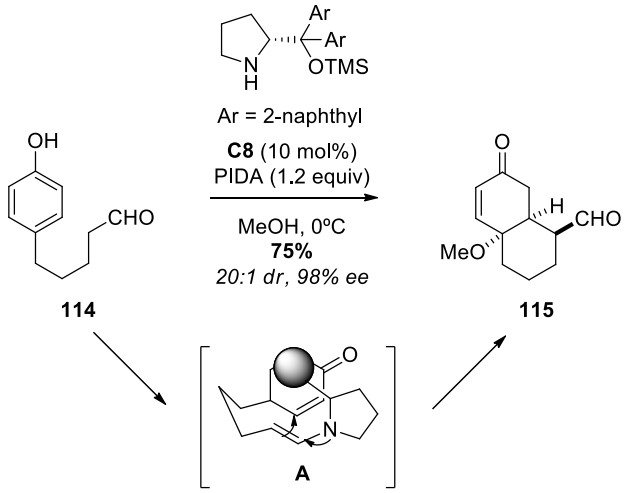
Organocatalytic desymmetrization.

Intramolecular Michael reactions.

Organocatalytic Michael additions have provided the basis for a large number of desymmetrization methodologies. In 2008, Gaunt and co-workers[79] published a one-pot dearomatization/Michael addition desymmetrization sequence using an organocatalytic

[78] Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-Q. *J. Am. Chem. Soc*. **2013**, *135*, 11700.
[79] Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 404.

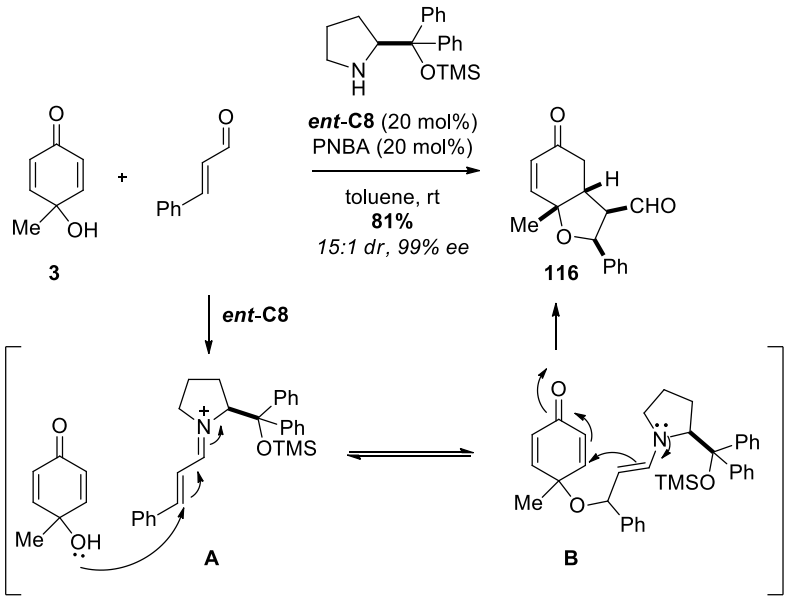
activation based on the formation of a chiral enamine (**Scheme 3.12**). In the best conditions reported, the treatment of *p*-hydroxyphenylpentanal **114** with 1.2 equivalents of PIDA in the presence of proline-derived catalyst **C8**, gave bicyclic product **115** in very good yield (75%), and diastereoselectivity (20:1 with respect to the all *cis*-substituted) with an excellent enantioselectivity (98% *ee*). The authors proposed that the high level of enantioselectivity is due to the bulky formation of an enamine **intermediate A**, which is hindering one of the double bond of the *p*-quinol towards the conjugate addition



Scheme 3.12

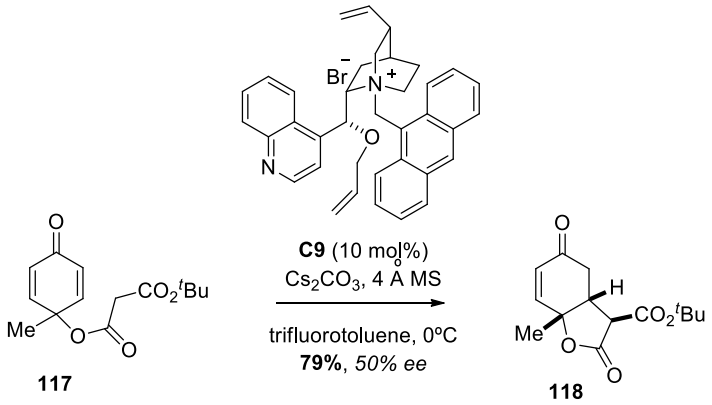
More recently, Johnson *et al*.[80] have reported an enantioselective desymmetrization of *p*-quinol **3** using the same diphenyl prolinal catalyst. In this case, the reaction of *p*-quinol **3** with cynnamaldehyde catalyzed by ***ent*-C8** gave bicyclic compound **116** with good yield and excellent diastereoselectivity and enantioselectivity (**Scheme 3.13**). The authors proposed that an intermolecular oxa-Michael addition of the hydroxyl group at C-4 of *p*-quinol to the α,β-unsaturated imininium salt **A**, generated by reaction of chiral amine ***ent*-C8** and cynnamaldehyde, is followed by the intramolecular 1,4-addition of the resulting enamine **B**. The chiral enamine is able to differenciate between both enantiotopic double bonds of the cyclohexadienone moiety.

[80] Corbett, M. T.; Johnson, J. S. *Chem. Sci*. **2013**, *4*, 2828.



Scheme 3.13

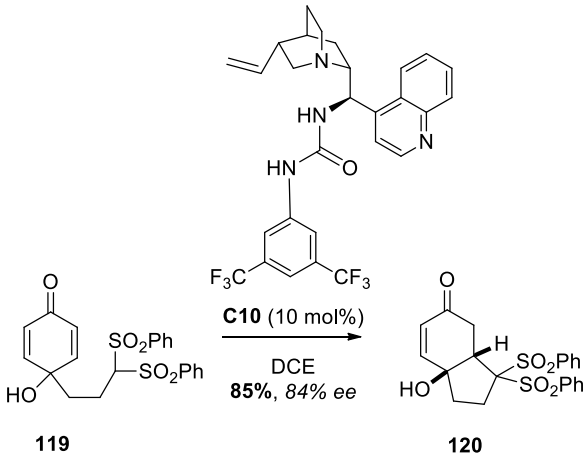
Harned[81] and co-workers, in 2011, reported the base-catalyzed enantioselective intramolecular 1,4-addition of *O*-malonate derived *p*-quinol **117** using Cinchona alkaloid **C9** as a phase transfer catalyst. The corresponding bicyclic lactones **118** were obtained in good yield and moderate enantioselectivity (50% *ee*) (**Scheme 3.14**).



Scheme 3.14

In 2011, You and co-workers[82] reported an enantioselective bifunctional-urea catalyzed Michael addition of substrates containing a 4-(3,3'-bis(phenylsulfonyl)) propyl group such as **119**. In this case, the chiral cinchone base urea catalyst **C10** mediated the formation of byciclic enone **120** in 85% yield and 84% *ee* (**Scheme 3.15**).

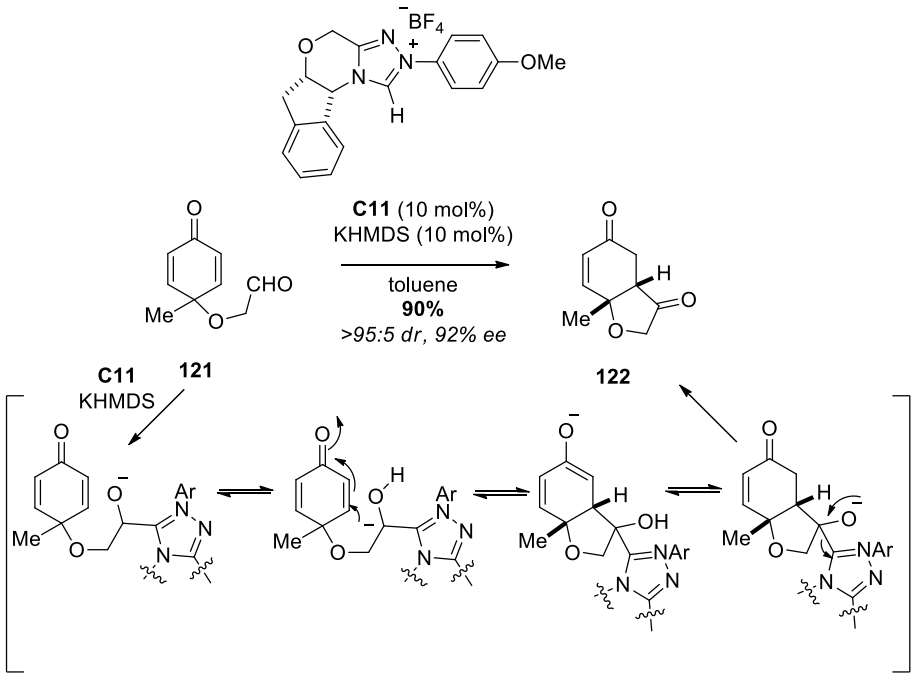
[81] Tello-Aburto, R.; Kalstabakken, K. A.; Volp, K. A.; Harned, A. M. *Org. Biomol. Chem*. **2011**, *9*, 7849.
[82] Gu, Q.; You, S.-L. *Org. Lett*. **2011**, *13*, 5192.



Scheme 3.15

Stetter reactions.

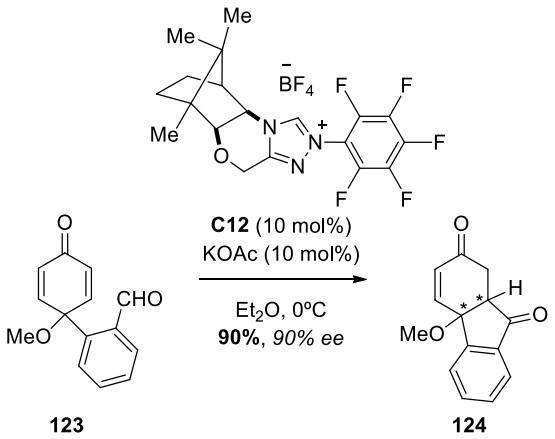
Rovis and co-workers[83] reported in 2006 the enantioselective synthesis of bicyclic diketones **122** in good yield with excellent stereocontrol from *O*-formylmethyl *p*-quinol **121** and chiral N-heterocyclic carbene **C11** by means of an intramolecular Stetter reaction[84] (**Scheme 3.16**).



Scheme 3.16

[83] Liu, Q.; Rovis, T. *J. Am. Chem. Soc*. **2006**, *128*, 2552.
[84] Stetter, H.; Schreckenberg, M. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 81.

A similar approach have been reported by You[85] and co-workers using the *N*-Heterocyclic carbene **C12** as catalyst for the intramolecular Stetter reaction between the aldehyde group present in **123** and the cyclohexadienone moiety. Tricyclic carbocycles (**124**) were obtained in excellent yield and enantioselectivity (**Scheme 3.17**).



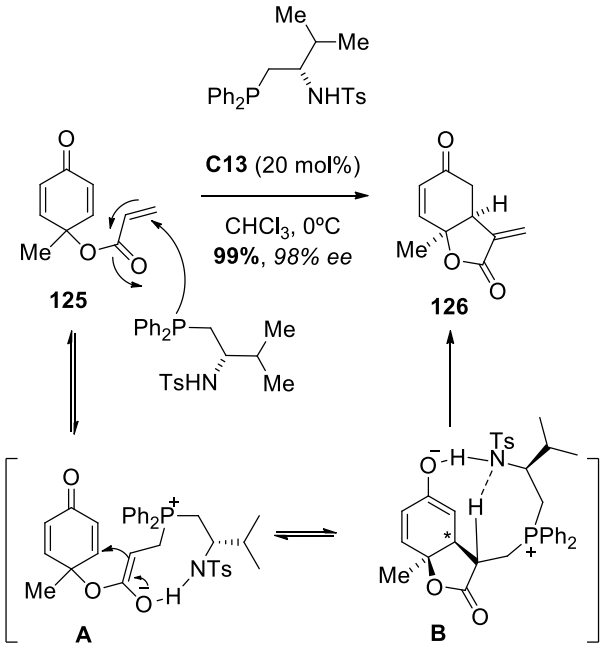
123 **124**

Scheme 3.17

Rauhut-Curier reactions.

Sasai and co-workers[86] reported the asymmetric Rauhut-Curier[87] reaction of cyclohexadienones bearing unsaturated esters **125** in the presence of chiral organocatalyst **C13**. substrates Bicyclic lactones **126** were obtained in good yields and high levels of enantioselectivity (**Scheme 3.18**). The proposed mechanism of the Rauhut-Curier reaction, using the chiral catalyst **C13** bearing both Brønsted acid (NHTs) and Lewis base (PPh_3) moieties, is initiated by the Michael-type addition of the phosphine moiety to the acrylate unit of **125** generating the phosphonium enolate **A**, which is stabilized by the Brønsted acid. This enolate **A** reacts with one of the two enantiotopic double bond of the cyclohexadienone, resulting in the formation of **intermediate B**. Finally, proton transfer from the α-position of a carbonyl group of the lactone to the enolate anion in **B** through the Brønsted acid moiety results in the formation product **126** (**Scheme 3.18**).

[85] Jia, M.-Q.; You, S.-L. *Synlett.* **2013**, 1201.
[86] (a) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423; (b) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Suzuki, M.; Enders, D.; Sasai, H. *Tetrahedron* **2013**, *69*, 1202.
[87] Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069.



Scheme 3.18

3.1.2. p-Quinols and heterocyles: synthesis, structures and properties.

Among the family of heteroaromatic compounds indoles[24] are known to be highly reactive and their core is embedded in many biological systems including the essential amino acid Tryptophan, the neurotransmitter Serotonin, and the mammalia hormone Melatonin or in many drugs such as Sumatriptan or Ondansetron (**Figure 3.1**).[25]

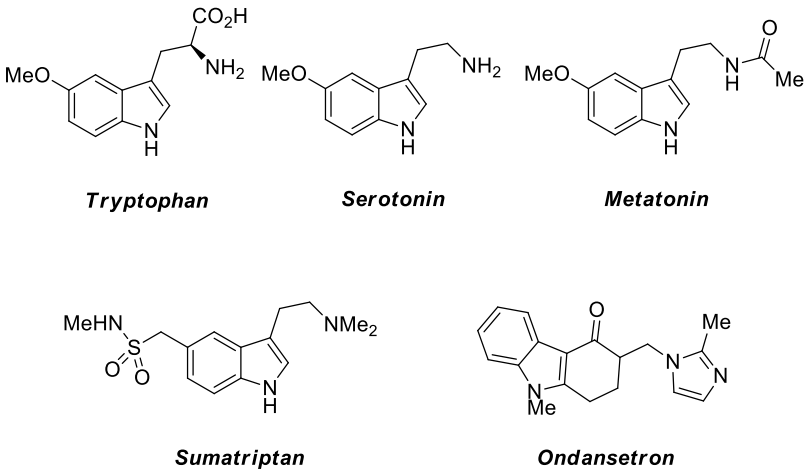


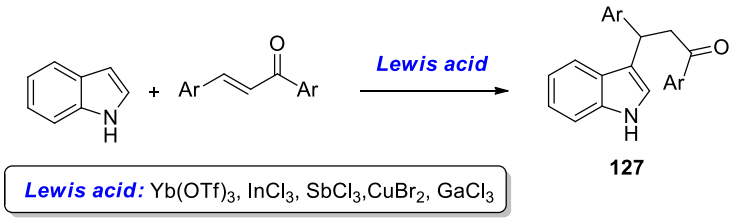
Figure 3.1

Moreover, indole is an excellent synthetic intermediate used in the preparation of other biological molecules. In this context, the Lewis acid promoted Friedel-Crafts[88] reaction of aromatic compounds is one of the most commun transformations developed by indoles. In particular, there are plenty examples related to the addition of indoles to electrophilic alkenes. Both protic and Lewis acids have been used as catalysts in this type of Friedel-Crafts reactions.

Conjugate additions of indoles to α,β-unsaturated systems.

Among the most used acidic catalysts in the Friedel Crafts reaction of indoles with different α,β-unsaturated enones, triflic acid,[89] polyvinylsulfonic acid,[90] Amberlyst sulfonic acid resins,[91] or silica-supported $NaHSO_4$[92] gave good results.

The first example of a Lewis acid-catalyzed addition of indoles to enones was developed by Kerr[93] *et al*. and used $Yb(OTf)_3$ as catalyst although other Lewis acids such as $InCl_3$,[94] $SbCl_3$,[95] $CuBr_2$,[96] and $GaCl_3$[97] have been also reported to give good yields with 1,3-diarylpropenones **127** (**Scheme 3.19**).



Scheme 3.19

---

[88] For a Friedel Crafts reaction revision see: a) Organic Synthesis (Ed.: M. B. Smith), McGraw-Hill, New York, **1994**, p. 1313. b) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. *Friedel-Crafts Alkylations* En *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. 3, pp 293. c) H. Heaney en *Comprehensive Organic Synthesis*, Vol. 2 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 733. d) R. M. Roberts, A. A. Khalaf, *Friedel-Crafts Alkylation Chemistry: A Century of Discovery,* Marcel Dekker, New York, **1984**. e) G. A. Olah, *Friedel-Crafts and Related Reactions*, Vol. II, part 1, Wiley-Interscience, New York, **1964**.

[89] Zhang, H.-B.; Liu, L.; Liu, Y.-L.; Chen, Y.-J.; Wang, J.; Wang, D. *Synth. Commun.* **2007**, *37*, 173.

[90] Ekbote, S. S.; Panda, A. G.; Bhor, M. D.; Bhanage, B. H. *Catal. Commun*. **2009**, *10*, 1569.

[91] Bandini, M.; Fagioli, M.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2004**, *346*, 545.

[92] Das, B.; Chowdhury, N.; Damodar, K.; Reddy, K. R. *Helv. Chim. Acta* **2007**, 90, 340.

[93] Harrington, P. E.; Kerr, M. A. *Synlett*, **1996**, 1047.

[94] Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165.

[95] Maiti, G.; Kundu, P. *Synth. Commun.* **2007**, *37*, 2309.

[96] Nayak, S. *Synth. Commun.* **2006**, *36*, 1307.

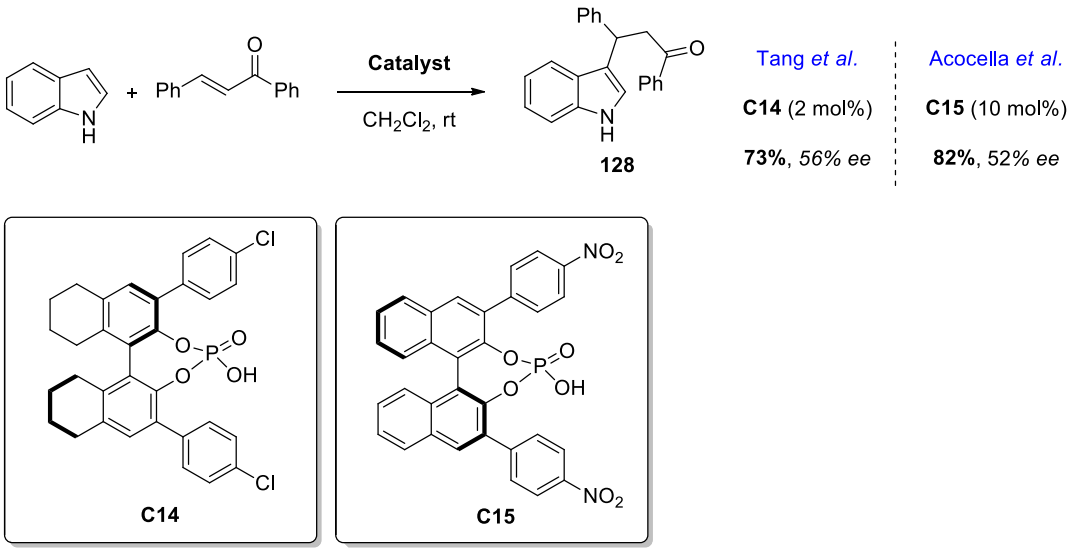
[97] Xu, R.; Ding, J. C.; Chen, X. A.; Liu, M. C.; Wu, H. Y. *Chin. Chem. Lett.* **2009**, *20*, 676.

$InBr_3$[98] gave good results with β-methyl, β-aryl and cyclic enones. $Bi(OTf)_3$[99] is one of the few catalysts reported to be successful for reactions with acrylate esters and acrylonitrile as well as with enones.

The enantioselective version for the conjugate addition of indoles to α,β-unsaturated enones have been explored, including both Lewis and Brønsted acids. Some metals such as Zr,[100] Al-salen complexes,[101] Sc,[102] Cu-oxazolidine complexes[103] or Zn[104] have been used in enantioselective reactions of differently substituted indoles to α,β-unsaturated systems. If we focus on the enantioselective reaction of indoles and conjugated systems using phosphoric acids as catalysts several examples have been developed. The first one, developed by Tang[105] *et al.*, afforded Friedel Crafts product **128** from indole 1H-indole and chalcone in good efficiency but with regular enantiomeric excess (up to 56% *ee*) through the use of the H8-BINOL-based phosphoric acid **C14** (**Scheme 3.20**). Acocella's[106] research group, taking into account that the different steric and electronic effects of the substituents in the chiral phosphoric acids were found exert a deep influence, both on efficiency and enantioselectivity, decided to investigate the catalytic properties of the 3,3'-bis-(4-nitrophenyl)-BINOL-phosphoric acid **C15** in the F.C. alkylation of 1H-indole with chalcones affording product **128** in regular to excellent yields and still regular enantiomeric excess (**Scheme 3.20**).

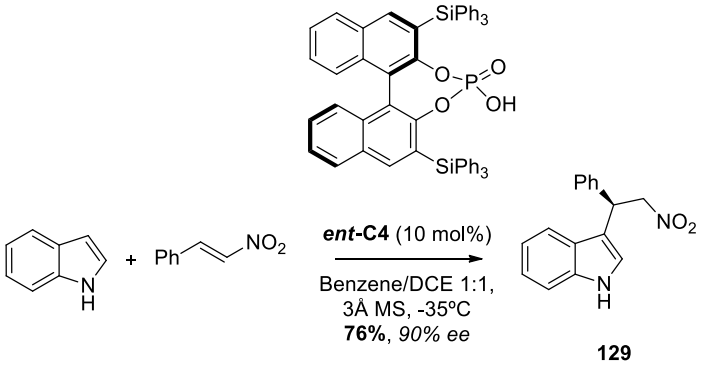
---

[98] Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700.
[99] Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett* **2003**, *44*, 5115.
[100] Blay, G.; Fernandez, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, 9, 2601.
[101] a) Bandini, M.; Fagioli, M.; Melchiorre, B.; Melloni, A.; Umani-Ronchi, A. (2003) *Tetrahedron Lett.* **2003** , *44*, 5843; b) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511.
[102] Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780.
[103] a) Barakat, A.; Islam, M. S.; Al Majid, A. M. A.; Al-Othman, Z. A. *Tetrahedron*, **2013**, *69*, 5185; b) Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3250.
[104] Jia, S.-J.; Du, D.-M. *Tetrahedron: Asymmetry* 2014, *25*, 980.
[105] Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H.; Zhao, G.-F.; He, L.-N.; Tang, C.-C. *Eur. J. Org. Chem.* **2008**, 1406.
[106] Scretti, A.; Villano, R.; Acocello, M. R.; *Molecules* **2009**, *14*, 3030.



Scheme 3.20

The enantioselective Friedel-Crafts alkylation of substituted indoles with nitrostyrene catalyzed by chiral BINOL-based phosphoric acid ***ent*-C4** was described by the research group of Itoh and Akiyama[107] affording product **129** in a quantitative yield and high enantioselectivities of up to 90% *ee* (**Scheme 3.21**).

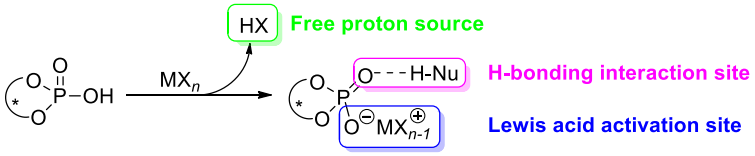


Scheme 3.21

In the literature it has been described the use of a binary catalyst constituted by a metal and a phosphoric acid derived of BINOL in the reaction of FC with indoles with enones. The cooperative catalytic system has a Lewis acid site for activating the electrophile, a base site for activating the nucleophile through a hydrogen-bonding interaction, and a free proton

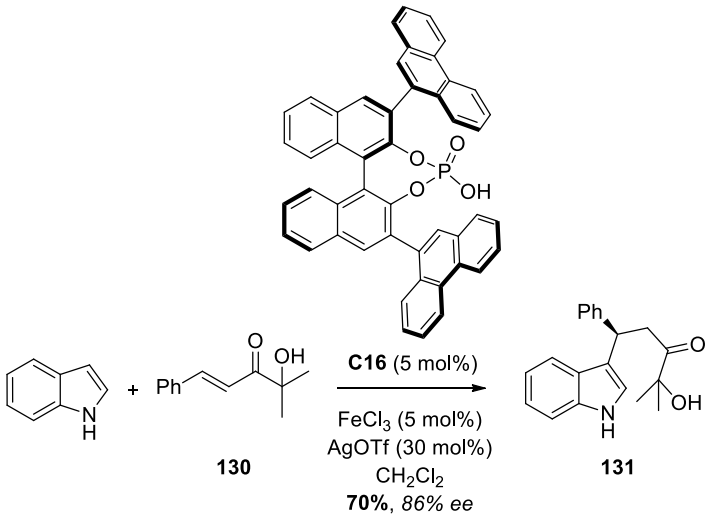
[107] Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4016.

source for accelerating the proton transfer from the nucleophile moiety (indole) to newly generated enolate (**Scheme 3.22**).



Scheme 3.22

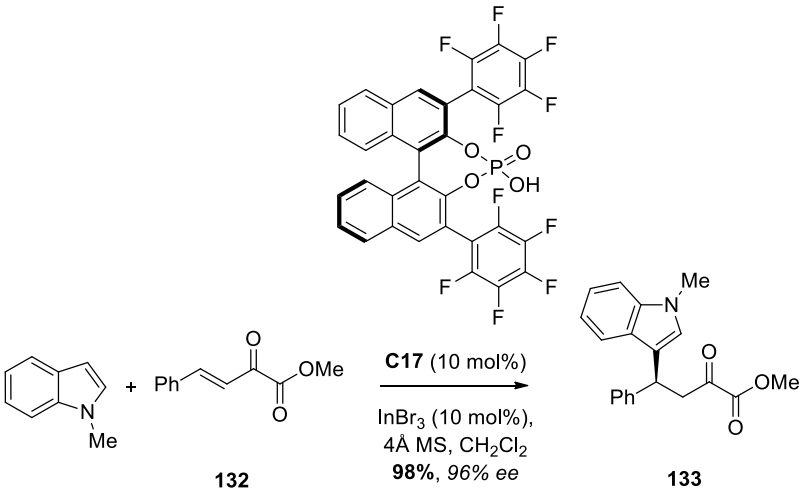
Based on the reactivity of these binary catalysts, in 2010, Huang[108] *et al.* reported the cooperative catalytic system established by the combination of an iron salt and the chiral phosphoric acid **C16** in the asymmetric Friedel-Crafts alkylation of indole with β-aryl α'-hydroxyenones **130** affording products **131** with good yields and enantioselectivities (**Scheme 3.23**).



Scheme 3.23

Cheng[109] *et al.* reported in 2011 the asymmetric binary acid catalyst that synergistically combined a chiral phospohoric acid **C17** and a indium halide salt to achieve 1,4-selective Friedel-Crafts alkylation of *N*-methyl protected indole with β,γ-unsaturated α-keto esters **132** affording products **133** with excellent reactivity and enantioselectivity (**Scheme 3.24**).

[108] Yang, L.; Zhu, Q.; Guo, S.; Qian, B.; Xia C.; Huang, H. *Chem. Eur. J.* **2010**, *16*, 1638.
[109] Lv, J.; Zhang, L.; Zhou, Y.; Nie, Z.; Luo, S.; Cheng, J-P. *Angew. Chem. Int. Ed.* **2011**, *50*, 6610.



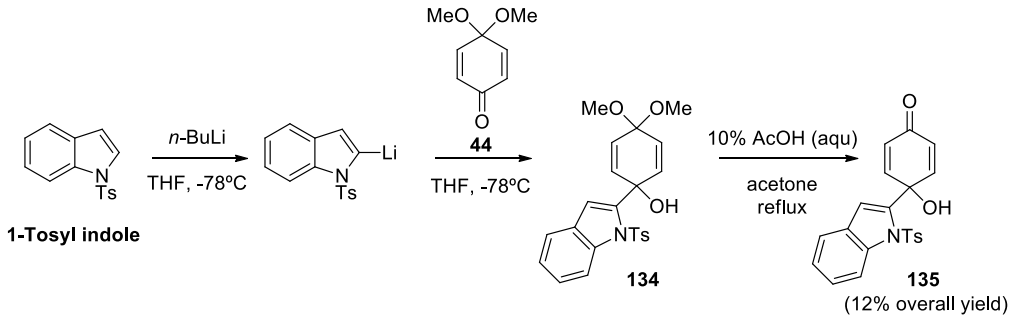
132 **133**

Scheme 3.24

Indoles bearing a 2,5-cyclohexadienone moiety derivatives.

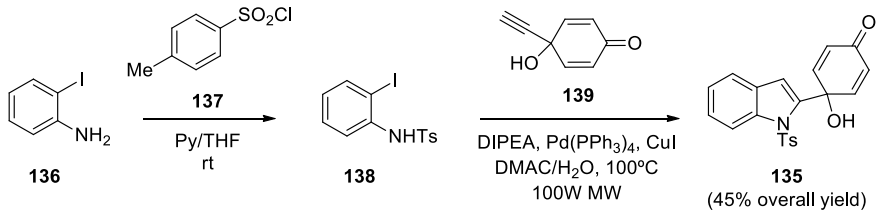
As it has been previously reported in this Ph D work, both *p*-quinols and indoles derivatives, have a huge importance due to their activity towards different diseases. The need to combine both moieties in the same molecule inspired Stevens' research group to describe the synthesis of a series of new heteroaromatic-substitued quinols. The generation of novel and structurally diverse chemical oxidation products of bioactive phenols as potential therapeutic agents with enhanced biological properties has led to the discovery of 4-hydroxycyclohexa-2,5-dienones substituted with a heterocyclic fragment in the 4-position, a new pharmacophore in anticancer drug development.

Thus, Stevens *et al.* have extensively studied the synthesis of *p*-quinol derivatives bearing an indole framework such as **135** by the lithiation[1d] of precursor heterocycles (in this case 1-Tosyl-indole) followed by their addition to *p*-benzoquinone dimethyl monoketal **44** generating the intermediate dimethyl ketal **134** which, after hydrolyzation affords *p*-quinol **159** (**Scheme 3.25**).



Scheme 3.25

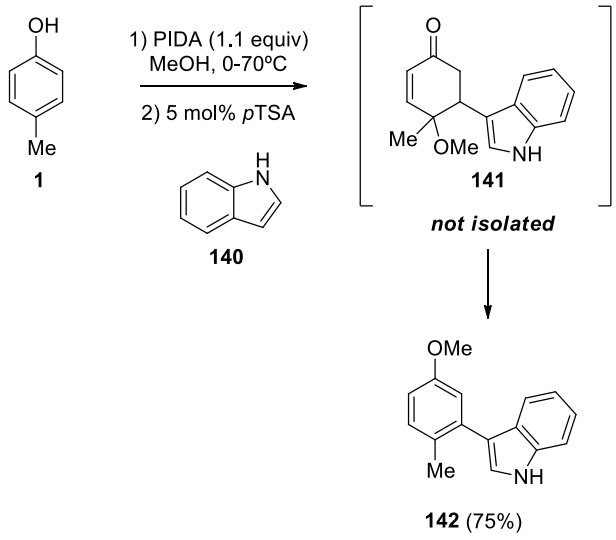
Due to the poor yields obtained with this methodology, this group described in 2007 the synthesis of 4-[1-(Arylsulfonyl-1H-indol-2-yl)]-4-hydroxycyclohexa-2,5-1-ones **135** by means of a Sonogashira reaction instead of the formation of the heteraryl lithium reagent (**Scheme 3.26**).[1c] 2-iodoaniline **138** activated by an N-arylsulfonyl residue was prepared from arylsulfonyl chloride **137** and 2-iodoaniline **136** in pyridine. Reaction of **138** with *p*-quinol **139** (bearing an alkynyl moeity) in an homogeneous catalyst system consisted by tetrakis(triphenylphosphine)palladium and copper iodide in a diisopropylamine (DIPEA)/ aqueous DMAC (Dimethylacetamide) medium at 100°C afforded indole **135** in a 45% overall yield in only 10 min with microwave irradiation.



Scheme 3.26

The importance to introduce the indole fragment into the quinol moiety in other different way than Stevens' synthesis represents a new challenge in quinol chemistry. Among all the conjugated addition reactions to *p*-quinols systems previously described there are no examples of a conjugated addition using a heteroaromatic reagent as nucleophile, despite its high reactivity in Friedel Crafts alkylation reactions.

In fact, the only example (**Scheme 3.27**) which uses indole derivatives (**140**) as nucleophiles in a conjugated addition to 4-methoxy-4-methylcyclohexen-2,5-dienone (generated *in situ* from *p*-alkyl phenol **1**) undergo an aromatization in situ and the FC alkylation product **141** could not be observed, only the FC arylation product (indolyl substituted O-methyl phenol) **142** was isolated in 75% yield.[26]



Scheme 3.27

3.1.3. Properties and synthesis of indeno[2,1-b]indoles and benzo[c]carbazoles.

When focusing in the intramolecular version of this reaction tetracyclic structures such as (octahydroindeno[2,1-*b*]indole) or angular structures such as (polyhydro-1H-benzo[*c*]carbazole) could be achieved (**Figure 3.2**).

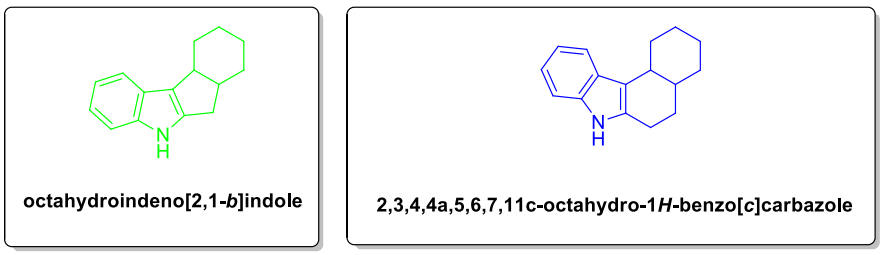


Figure 3.2

The octahydroindeno[2,1-*b*]indole structure is present in the fischerindole class of natural products which present inhibitory activity against representative bacterial, fungal and mycobacterium species (**Figure 3.3**).[110]

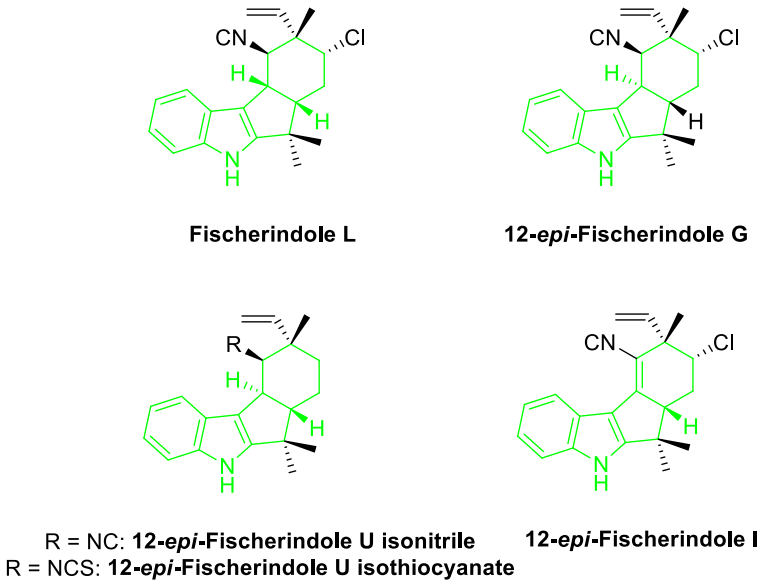
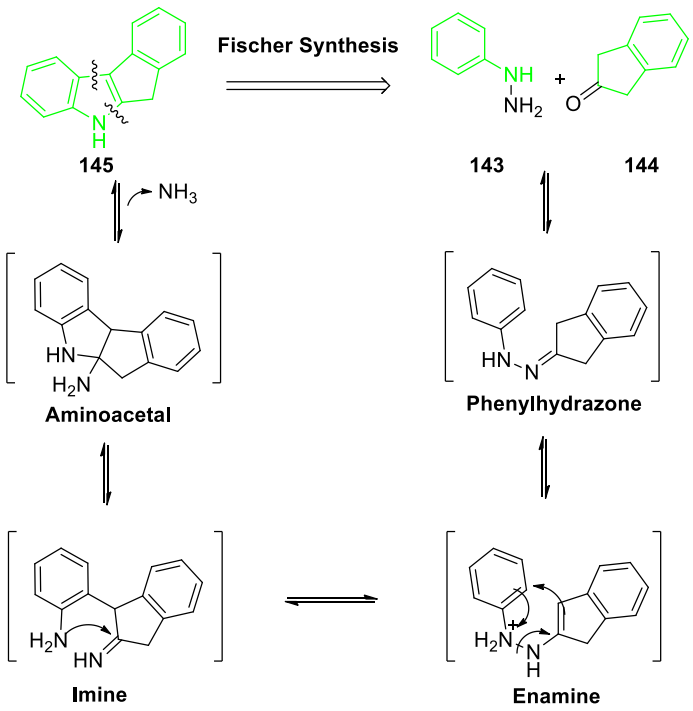


Figure 3.3

More oxidized derivatives **145** with 5,10-dihydroindeno[1,2-*b*]indole structure are shown to act as strong antioxidants[111] and they can mainly be synthetized by the Fischer indolisation[112] of phenylhydrazines **143** and indan-2-ones **144** in an acidic medium. The reaction of a phenyl hydrazine **143** with indan-2-one **144** initially forms a phenyl hydrazone which isomerizes to the respective enamine. After protonation, a cyclic [3,3]-sigmatropic rearrangement occurs producing an imine. The resulting imine forms a cyclic aminoacetal, which under acid catalysis eliminates NH_3, resulting in the energetically favorable aromatic 5,6-dihydroindeno[2,1-b]indole **145** (**Scheme 3.28**).

[110] (a) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257; (b) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938; (c) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 7450.
[111] Brown, D. W.; Graupner, P. R.; Siansbury, M.; Shertzer, H. G. *Tetrahedron* **1991**, *47*, 4383.
[112] Brown, D. W.; Mahona, M. F.; Ninana, A.; Sainsbury, M.; Shertzer, H. G. *Tetrahedron* **1993**, *49*, 8919.



Scheme 3.28

Benzo[*c*]carbazole, albeit rare in nature, is an important structural motif in medicinal and materials chemistry[113] (**Figure 3.4**). An example of their activity is benzo[*c*]carbazole **146** synthetically obtained which shows promising profiles for intra-cyclin dependent kinase selectivity (**Figure 3.4**).

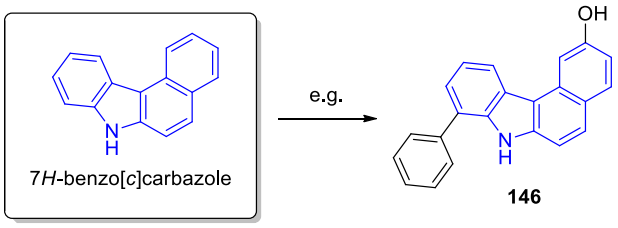
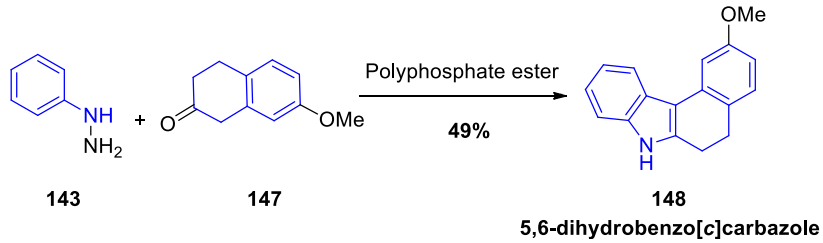


Figure 3.4

Efforts have thus been devoted toward developing general and efficient synthetic methods for the synthesis of benzo[*c*]carbazoles. In 1966 and based on Fischer synthesis, the group of Yonemitsu[114] developed the synthesis of some 5,6-dihydrobenzo[*c*]carbazoles such as

[113] For a review on carbazoles and benzo[*c*]carbazoles in part: Knolker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303; For a leading reference on the medicinal application, see: Buchgraber, P.; Domostojj, M. M.; Scheiper, B.; Wirtz, C.; Mynott R.; Rust, J.; Fürstner, A. *Tetrahedron* **2009**, *65*, 6519; For an application to materials chemistry, see: Zafer, C.; Gultekin, B.; Ozsoy, C.; Tozlu, C.; Aydin, B.; Icli, S. *Sol. Energy Mater. Sol. Cells* **2010**, *94*, 655.

148 using polyphosphate ester as catalyst for the condensation of β-tetralone **147** with phenylhydrazine **143** (**Scheme 3.29**).

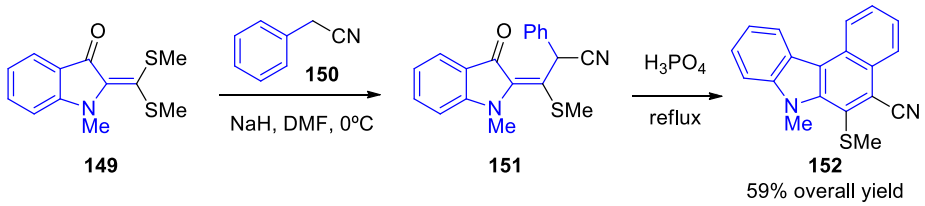


143 **147** **148**

5,6-dihydrobenzo[*c*]carbazole

Scheme 3.29

In 1999, Ila and Junjappa[115] *et al.* reported the synthesis of the benzo[*c*]carbazole **152**. This approach uses *N*-methyl 2-bis(methylthio)methylene-3-oxoindole **149** as electrophilic reagent. The addition of the anion of phenylacetonitrile **150** to the 3-oxoindole **149** afforded compound **151** by elimination of methanethiol. Cycloaromatization of **151** was again achieved by heating in the presence of phosphoric acid and provided the benzo[*c*]carbazole **152** in 59% overall yield (**Scheme 3.30**).



149 **151** **152**

59% overall yield

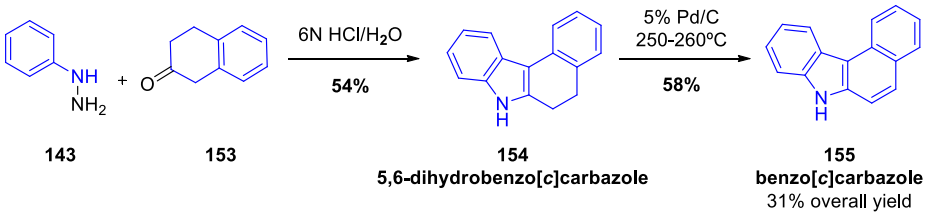
benzo[*c*]carbazole

Scheme 3.30

In 1988, Katritzky[116] *et al.* applied the Fischer indolization between hydrazine **143** and tetralone **153** for the synthesis of the benzo[*c*]carbazole **155** after a dehydrogenation step of 5,6-dihydrobenzo[*c*]carbazole **154** over chloranil or palladised charcoal, affording **155** in a moderate overall yield of 31% (**Scheme 3.31**).

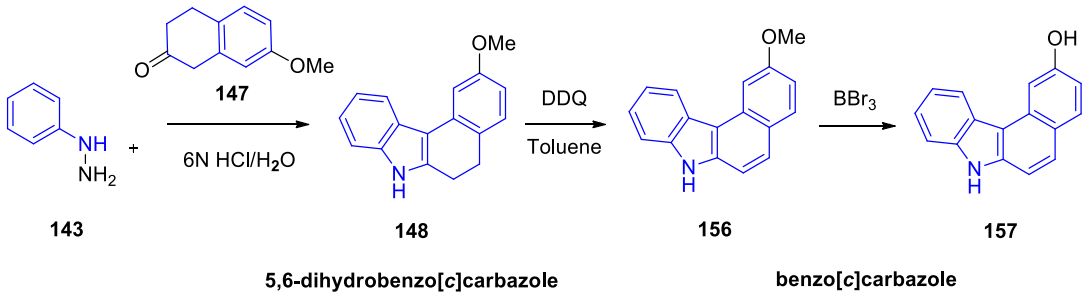
---

[114] Kanaoka, Y.; Ban, Y.; Miyashita, K.; Irie, K.; Yonemitsu, O. *Chem. Pharm. Bull.* **1966**, *14*, 934.
[115] Rao, M. V. B.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *Tetrahedron* **1999**, *55*, 11563.
[116] Katritzky, A. R.; Wang, Z. *J. Heterocyclic Chem.* **1988**, *25*, 671.



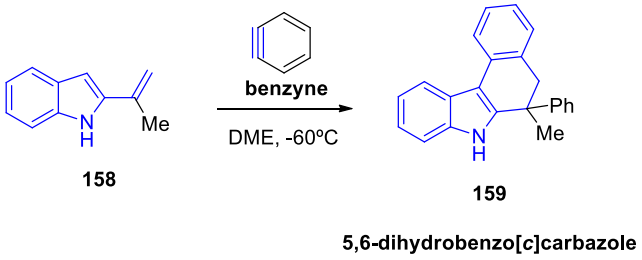
Scheme 3.31

Then, in 2001, 2-hydroxy-benzo[*c*]carbazoles such as **157** were achieved by a final oxidation step of 5,6-dihydrobenzo[*c*]carbazole **148** with DDQ and a methyl removal of the resulting 2-methoxy-benzo[*c*]carbazole **156** with BBr_3 from the condensation of phenylhydrazine **143** with 7-methoxy-β-tetralone **147**[117] (**Scheme 3.32**).



Scheme 3.32

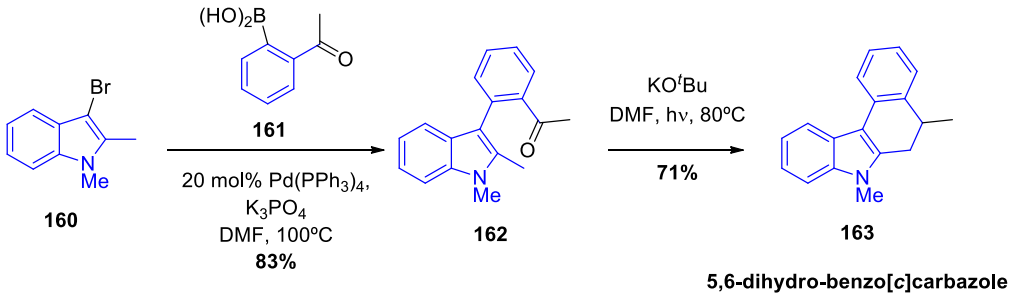
In 1991, Pindur[118] and co-workers described the synthesis of 5,6-dihydro-7*H*-benzo[*c*]carbazoles such as **159** by using 2-vinylindoles **158** for the Diels-Alder reaction with benzyne. The 2-vinylindoles **158** were added to in situ generated benzyne in dimethoxyethane (DME) at -60 °C to give the 5,6-dihydro-7*H*-benzo[*c*]carbazoles **159** with a phenyl group in the 6-position. These products are believed to be the result of an ene reaction of the initially formed cycloadduct with a second molecule of benzyne (**Scheme 3.33**).



Scheme 3.33

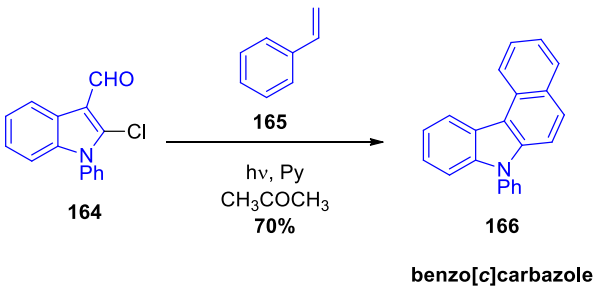
[117] Carini, D. J.; Kaltenbach, R. F.; Liu, J.; Benfield, P. A.; Boylan, J.; Boisclair, M.; Brizuela, L.; Burton, C. R.; Cox, S.; Grafstrom, R.; Harrison, B. A.; Harrison, K.; Akamike, E.; Markwalder, J. A.; Nakano, Y.; Seitz, S. P.; Sharp, D. M.; Trainor, G. L.; Sielecki, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2209.
[118] Pindur, U.; Pfeuffer, L.; Eitel, M.; Rogge, M.; Haber, M. *Monatsh. Chem*. **1991**, *122*, 291.

Koning[119] developed in 2006 a novel synthesis starting from simple indole precursors. Key steps included the use of the Suzuki-Miyaura reaction of indole **160** and boronic acid **161** to afford 3-aryl substituted indole **162** in 83% yield. The addition of potassium ^{t}butoxide in the light assisted aromatic ring-forming reaction, afforded 5,6-dihydrobenzo[*c*]carbazole **163** in moderate 71% yield (**Scheme 3.34**).



Scheme 3.34

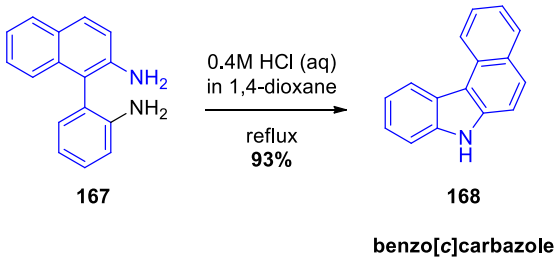
The one-pot synthesis of benzo[*c*]carbazoles **166** by photochemical annulation of 2-chloroindole-3-carbaldehydes **164** with styrenes **165** was developed by Shi[120] in 2008 (**Scheme 3.35**). The reaction occurred via photodechlorination-initiated coupling of 2-chloroindole-3-carbaldehyde with styrene. Then, the electrocyclic reaction and the deformylative aromatization in the presence of pyridine afforded derivative **166** in 70% isolated yield.



Scheme 3.35

[119] Pathak, R.; Nhlapo, J. M.; Govender, S.; Michael, J. P.; van Otterlo, W. A. L.; Koning, C. B. *Tetrahedron* **2006**, *62*, 2820.
[120] Wang, C.; Zhang, W.; Lu, S.; Wu, J.; Shi, Z. *Chem. Comm.* **2008**, 5176.

Cho[121] *et al.* reported in 2011 the acid-catalysed condensation of 2,2'-diamino-1,1'-biaryls for the synthesis of benzo[*c*]carbazole **168**. 2-2'-diamino-1,1'-biaryl **167** were found to undergo ring-closure condensation reaction to afford **168** in good to excellent yields, in this case 93% isolated yield (**Scheme 3.36**).



167 **168**

benzo[*c*]carbazole

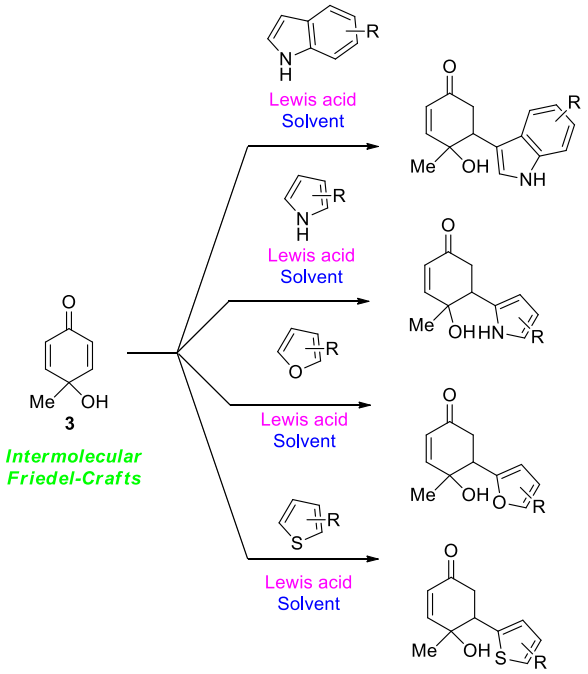
Scheme 3.36

[121] Lim, B.-Y.; Choi, M.-K.; Cho, C.-G. *Tetrahedron Lett.* **2011**, *52*, 6015.

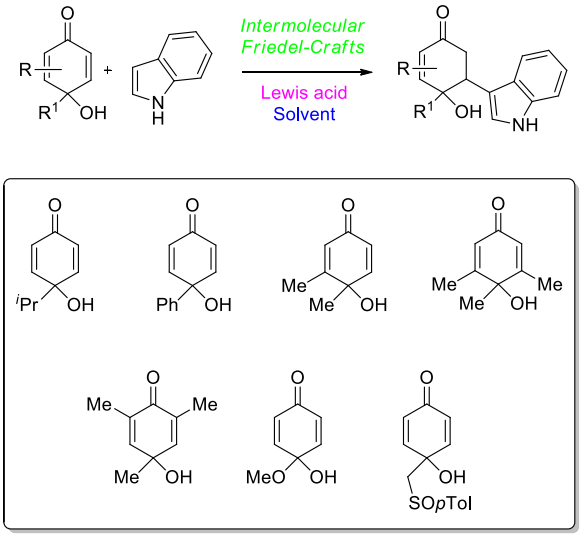
OBJECTIVES

With the aim to synthetize structures which combine both, the *p*-quinol core and the indolyl core, from a conjugated addition reaction and regarding the excellent results obtained in our research group in the carbon nucleophile conjugate addition to *p*-quinols, we established as the objectives of this Chapter as:

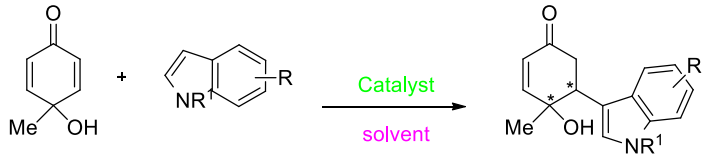
The study of the intermolecular conjugated addition of heteroaromatic nucleophiles to 2,5-cyclohexadienone **3** optimizing both the Lewis acid and the solvent.



The study of the intermolecular reaction of indole with different 2,5-cyclohexadienones systems under the optimized conditions

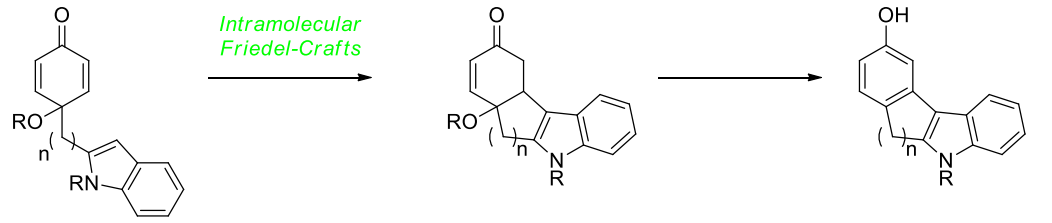


The study of the enantioselective reaction of *p*-quinol **3** and different indoles using a chiral catalyst



3

The synthesis and study of the intramolecular Friedel-Crafts reaction of 4-(2-indolylalkyl)quinols in order to obtain the FC alkylated and FC arylated products.



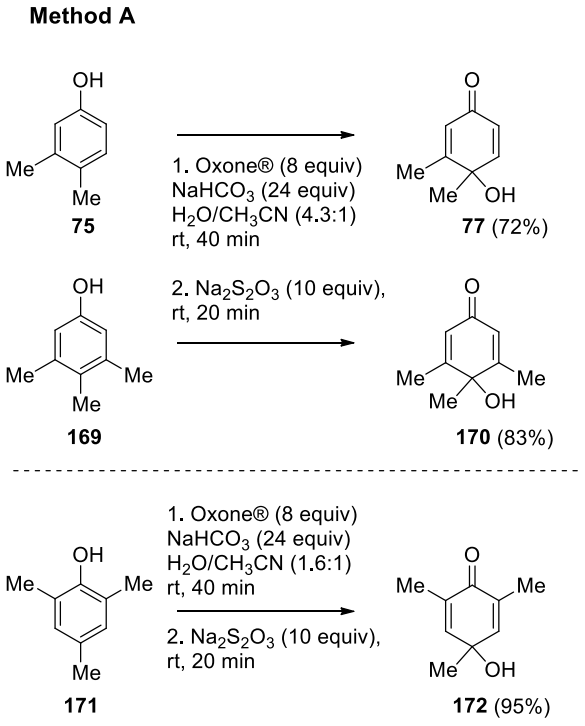
4-(2-indolylalkyl)quinols ***FC alkylated products*** ***FC arylated products***

3.2. Results.

3.2.1. Intermolecular Friedel-Crafts reactions of different heteroaromatic derivatives with p-quinols.

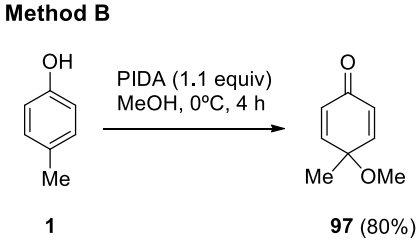
Synthesis of starting materials.

Unsubstituted *p*-quinol **3** was prepared following the methodology described in Chapter 2.[36] The synthesis of methyl substituted *p*-quinols **77**, **170** and **172** was achieved following the previously described **Method A** for the oxidative dearomatization of *p*-alkylphenols **75**, **169** and **171** respectively using Oxone®/$NaHCO_3$ as the source of singlet oxygen, in a mixture of H_2O/CH_3CN, following by reduction of the *p*-peroxyquinols intermediates with $Na_2S_2O_3$. 3-Methyl-*p*-quinol **77** and 3,5-dimethyl-*p*-quinol **170** were obtained in a 72% and 83% isolated yields respectively using a 4.3:1 mixture of H_2O/CH_3CN, while 2,6-dimethyl-*p*-quinol **172** was obtained using a 1.6:1 mixture of H_2O/CH_3CN in a 95% isolated yield (**Scheme 3.37**).



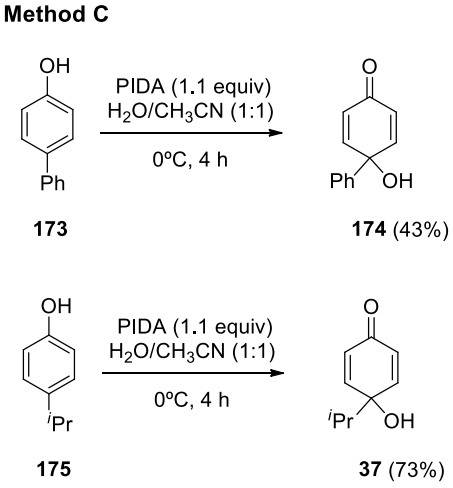
Scheme 3.37

The methyl ether derivative 4-methyl-4-methoxy-cyclohexa-2,5-dienone **97**[122] was obtained in 80% isolated yield from *p*-cresol **1** using 1.1 equivalents of a iodine hypervalent reagent (PIDA: Phenyl Iodonium Diacetate) and MeOH as solvent at 0°C (**Method B**) (**Scheme 3.38**).



Scheme 3.38

Following an analogous methodology, 4-phenyl and 4-*iso*-propyl-*p*-quinols **174**[123] and **37**[124] were synthetized from the corresponding phenols **173** and **175** using PIDA as the oxidant and H_2O/CH_3CN as solvent in a 43% and 73% yield respectively (**Method C**) (**Scheme 3.39**).

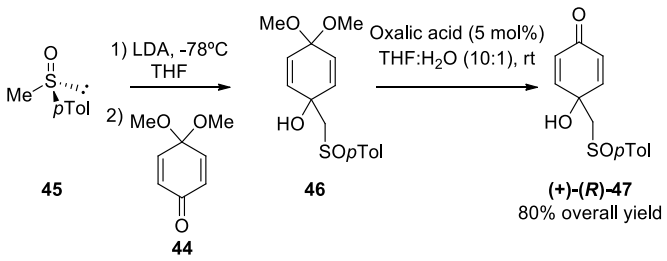


Scheme 3.39

Enantiopure (+)-(*R*)-(*p*-tolylsulfinyl)methyl-*p*-quinol 47 was synthetised following the methodology described in our group[48]ref cruzada from *p*-benzoquinone dimethyl monoketal 44 and methyl *p*-tolylsulfoxide 45. The addition of the lithium anion of methyl-*p*-tolylsulfoxide, previously generated with LDA in THF, to the benzoquinone monoketal 44 at -78°C afforded

[122]Ohkata, K.; Tamura, Y.; Shetuni, B. B.; Takagi, R.; Miyanaga, W.; Kojim, S.; Paquette, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 16783.
[123] Novak, M.; Glover, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7748.
[124] Tello-Aburto, R.; Kalstabakken, K. A.; Volp, K. A.; Harned, A. M. *Org. Biomol. Chem.* **2011**, *9*, 7849.

the intermediate ketal 46 that was directly hydrolyzed using a catalytic amount of oxalic acid (5mol%) in a THF:H_2O (10:1) solution to obtain the *p*-quinol 47 with an overall yield of 80% (**Scheme 3.40**).



Scheme 3.40

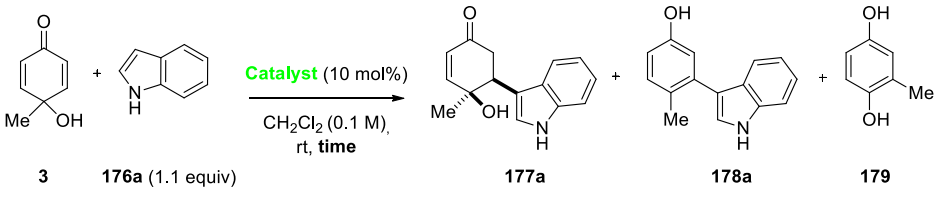
Racemic conjugate addition of heteroaromatic derivatives to p-quinols.

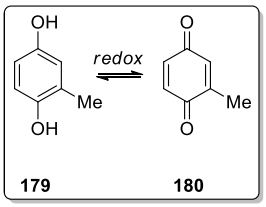
Conjugate addition reactions of indoles on *p*-quinols.

We iniatilly focused our study on the reaction of 1H-indole **176a** with *p*-quinol **3** (**Table 3.2**). The reaction between **176a** and **3** using CH_2Cl_2 (0.1 M) as solvent without any added catalyst at room temperature did not give any desired product, recovering the starting materials unaltered after 5 days (**Table 3.2, entry 1**). At the outset of this study we were pleased to find that treatment of 1H-indole **176a** with *p*-quinol **3** in the presence of $FeCl_3 \cdot 6H_2O$ (10 mol%), gave after 5 days, the Friedel Crafts (FC) product, as a mixture of the alkylated **177a** and arylated **178a** compounds, together with 2-methyl hydrobenzoquinone **179** in a 70:10:20 ratio of **177a**/**178a**/**179** measured by Gas Chromatography and Mass Spectroscopy (GC-MS) analysis of the crude mixture. The Friedel Craft alkylated product, 5-indolyl-2-ciclohexenone **177a** was obtained as a unique diastereoisomer in a 50% isolated yield (**Table 3.2, entry 2**), and 3-indolyl-4-methylphenol **178a** in 10% yield. To our surprise, using anhydrous $FeCl_3$, as catalyst, no FC reaction was observed and only **179** and 2-methyl-*p*-benzoquinone **180** products were obtained in a 1:4 ratio (**Table 3.2, entry 3**). In order to improve the yield of the FC alkylated product **177a**, other Lewis catalysts were tested (**Table 3.2, entries 4-7**). In all cases, unless otherwise noted, the *p*-quinol **3** and the catalyst were dissolved in CH_2Cl_2 at room temperature and (1H)-indole **176a** was added to the solution.

The reaction using $Fe(OTf)_3$ as catalyst provides a mixture of **177a/178a/179 in a** 48:4:48 ratio obtaining **177a** in 52% conversion (**Table 3.2, entry 4**). The use of a Fe (II) catalyst, such as $Fe(OAc)_2$, kept the starting materials unaltered (**Table 3.2, entry 5**). Using $Cu(OTf)_2$ as a cooper Lewis acid source, a 1:1 ratio of **177a/178a** was obtained with a 66% of conversion after 3 days (**Table 3.2, entry 6**). When the reaction was carried out in the presence of the brønsted acid *p*-toluenesulfonic acid (*p*TSA) (10 mol%) the FC arylated compound, 3-indolyl-4-methylphenol **178a**, was exclusively obtained in 70% isolated yield (**Table 3.2, entry 7**).

Table 3.2: Screening of catalysts





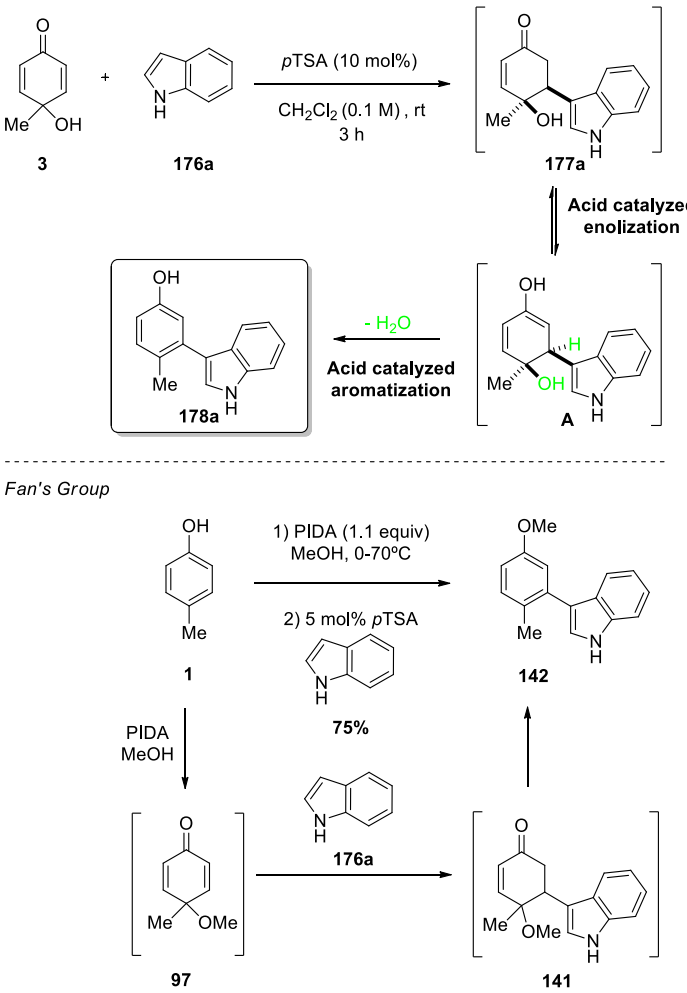
Entry	Catalyst	Time	**177a/178a/179** (%)[a]	Conversion to FC (%)
1	-	5 d	-	-
2	$FeCl_3{\cdot}6H_2O$	5 d	70/20/10	90 (50% yield of **177a**)
3	$FeCl_3$	3 d	0/0/100[b]	-
4	$Fe(OTf)_3$	3 d	48/4/48	52
5	$Fe(OAc)_2$	3 d	0/0/0	0
6	$Cu(OTf)_2$	3 d	33/33/0	66
7	*p*TSA	1 d	0/100/0	>98 (70% yield of **178a**)

[a] Ratio measured by GC-MS; [b] 80% **180** /20% **179**.

Table 3.2

Probably, in this last case, once the conjugate addition product is formed, the acidity of the medium facilitates the enolization of the intermediate and the elimination of H_2O (**Scheme 3.41**). Similar results were describe by Fan´s group[26] in the reaction between 4-alkylphenols such as **1**, indoles and hypervalent iodine (PIDA) in the presence of catalytic *p*TSA using MeOH as solvent. In this case, the authors proposed a domino sequence that begins with an oxidative dearomatization of the 4-alkylphenol **1** to *in situ* generate the 4-methoxy-*p*-quinol

intermediate **97**, the conjugate addition of the indole takes place over the cyclohexadiendione system affording intermediate **141**. An aromatization reaction with loss of MeOH takes place followed by the addition of MeOH to the carbonyl system and finally the loss of water, favored by the acid medium, gave 3-indolyl-4-alkyl-phenol **142** (**Scheme 3.41**).



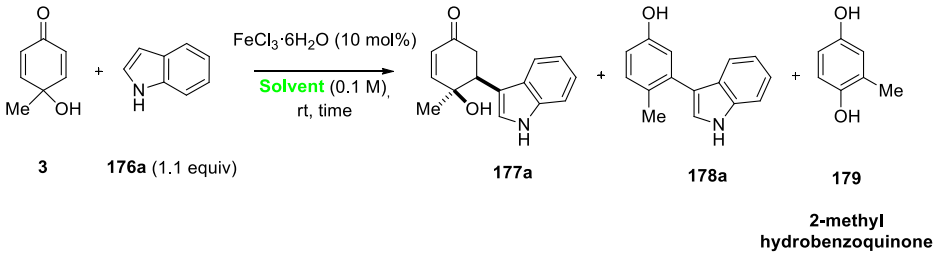
Scheme 3.41

With these initial results, we decided to continue the optimization study of the FC reaction keeping $FeCl_3 \cdot 6H_2O$ as the catalyst and survey the influence of solvents, catalyst loading, the addition order, concentration and temperature.

Different polar solvents (0.1 M) such as $CHCl_3$, CH_3CN, AcOEt, or DCE were screened, however no of them gave better results in terms of FC conversion as the initial CH_2Cl_2. The results are summarized in **Table 3.3**. The reaction using $CHCl_3$ was completed after 2 days to give the alkytated and arylated FC compounds **177a** and **178a** in a 65:16 ratio, together with a 19% of 2-methylhydroquinone **179** (**Table 3.3, entry 2**). When CH_3CN was used as solvent,

after 2 days, a 53:26:7 mixture of **177a/178a/179** was obtained and a 14% of starting material was recovered unaltered (**Table 3.3, entry 3**). When the reaction was set up using AcOEt as solvent after 2 days the FC arylated 3-indolyl-4-methylphenol **178a** was exclusively obtained (**Table 3.3, entry 4)**. To our surprise, using dichloroethane (DCE) as solvent, only hydroquinone **179** was recovered after 2 days (**Table 3.3, entry 5**).

Table 3.3: Screening of solvents



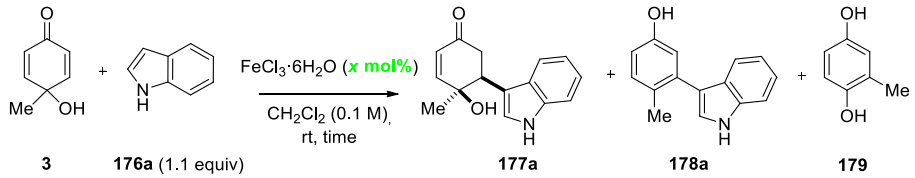
Entry	Solvent	Time	**177a/178a/179** [a]	Conversion to FC (%)
1	CH_2Cl_2	5 d	70/20/10	90 (50% yield of **177a**)
2	$CHCl_3$	2 d	65/16/19	81
3	CH_3CN	2 d	53/26/7[b]	79
4	AcOEt	2 d	0/100/0	>98
5	DCE	2 d	-/-/100	-

[a] Ratio measured by GC-MS, starting *p*-quinol complete the 100% ration of entry 3; [b] 2-methyl-benzoquinone form **180**; [c] 70:30 ratio **179**/**180**

Table 3.3

We next studied the catalyst loading, keeping the $FeCl_3·6H_2O$ as the Lewis acid, CH_2Cl_2 (0.1 M) as solvent at room temperature (**Table 3.4**). A decrease of the catalytic amount from 10 mol% to 5 mol% and 2 mol% was harmful for the reaction outcome, because after 14 h the 2-methyl-1,4-hydroquinone **179** was observed as the major product together with a 20-10% of the corresponding 2-methyl-1,4-benzoquinone **180** (**Table 3.4, entries 1 and 2**). The use of an equimolecular amount of $FeCl_3·6H_2O$ was also detrimental, and only a 7% of the 3-indolyl-4-methylphenol **178a** was obtained together with a 93% of the 1,4-hydroquinone derivative **179** (**Table 3.4, entry 4**). Consequently, we stabilized the used of 10 mol% of $FeCl_3·6H_2O$ as the best catalyst loading (**Table 3.4, entry 3**).

Table 3.4: Screening of the catalyst amount



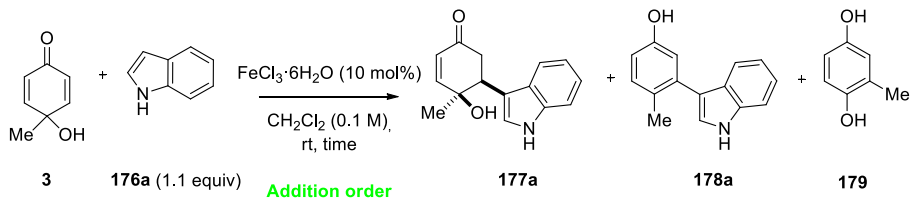
Entry	*x* mol%	Time	**177a**/**178a**/**179** [a]	Conversion to FC (%)
1	2	14 h	0/0/80[b]	-
2	5	14 h	0/0/93[c]	-
3	10	5 d	70/20/10	90 (50% yield of **201a**)
4	100	14 h	0/7/93	7

[a] Ratio measured by GC-MS, starting *p*-quinol complete the 100% ratio of entries1 and 2; [b] 80:20 **179**/**180**; [c] 90:10 ratio **179**/**180**.

Table 3.4

We next tested different variations on the addition order of the reagents. Until now the indole **176a** was added over a preformed solution of *p*-quinol **3** and $FeCl_3 \cdot 6H_2O$ (10 mol%) to give a 70:20:10 ratio of the FC alkylation, FC arylation and hydroquinone derivatives respectively (**Table 3.5, entry 1**). When all the reagents and the catalyst were added at once, the hydroquinone **179** was not observed, however the ratio of FC alkylated versus arylated compound turned to 65:35 (**Table 3.5, entry 2**). The addition of the *p*-quinol **3** to a preformed solution of indole **176a** and the iron catalyst gave exclusively the FC alkylated compound **177a**, although with a slightly decrease of the conversion (**Table 3.5, entry 3**). Finally, the best results in term of efficiency, conversion and yield were obtained when the $FeCl_3 \cdot 6H_2O$ was added to a solution of the *p*-quinol **3** and indole **176a**. In this case, all the *p*-quinol reacted with the indole in 19 h, and only a 8% of the FC arylated 3-indolylphenol **178a** was observed. Under these conditions the desired FC alkylated compound **177a** was obtained in a 91% isolated yield (**Table 3.5, entry 4**).

Table 3.5: Screening of the addition order



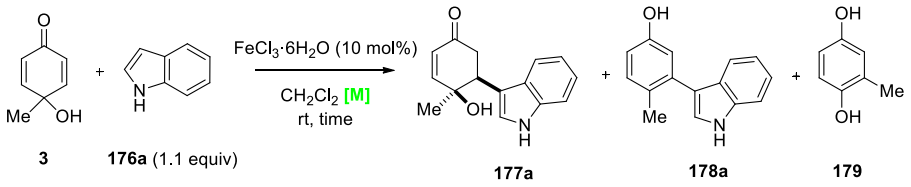
Entry	Time	**177a**/**178a**/**179** (%)[a]	Conversion to FC (%)
1[b]	5 d	70/20/10	90 (50% yield of **177a**)
2[c]	3 d	65/35/0	>98
3[d]	3 d	85/0/0	85
4[e]	19 h	92/8/0	>98 (91% yield of **177a**)

[a] Ratio measured by GC-MS, the starting *p*-quinol complete the 100% ratio of entry 3; [b] Indole **176a** was added to a solution of $FeCl_3 \cdot 6H_2O$ and *p*-quinol **3**; [c] All the reactants were added at the same time; [d] *p*-quinol **3** was added to a solution of $FeCl_3 \cdot 6H_2O$ and indole **176a**; [e] $FeCl_3 \cdot 6H_2O$ was added to a solution of *p*-quinol **3** and indole **176a**

Table 3.5

We next tested different concentrations of the reaction from 0.1 to 0.5 M (**Table 3.6**). When the process was developed at 0.5 M, a complete conversion was observed after 7 hours and a 87:13 ratio of the FC alkylated/arylated compounds **177a** and **178a** was obtained (**Table 3.6**, **entry 1**). More concentrated reactions (up to 1 M) gave lower conversions and increased the degradation of the *p*-quinol to the hydroquinone **179** (**Table 3.6, entry 2**). Lower concentrations (0.05 M) gave similar results as the initial 0.1 M reaction (**Table 3.6**, **entries 4 and 3** respectively). Therefore, we followed our study with 0.1 M concentrations.

Table 3.6: Screening of the concentration [M]



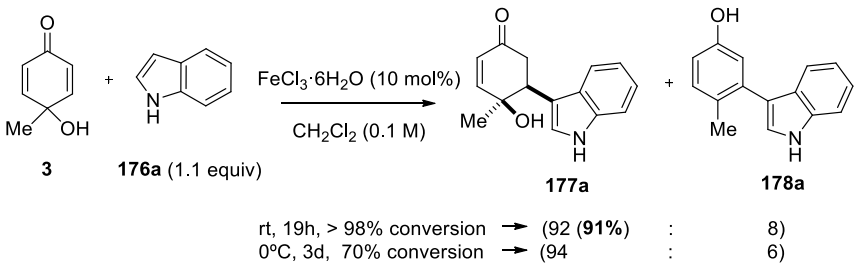
Entry	[M]	Time	**177a**/**178a**/**179** (%)[a]	Conversion to FC (%)
1	0. 5	7 h	87/13/0	>98
2	1	16 h	31/0/63[b]	31
3	0.1	19 h	92/8/0	>98 (91% yield of **179a**)
4	0.05	16 h	92/8/0	>98

[a] Ratio measured by GC-MS, the starting *p*-quinol complete the 100% ratio of entry 2 [b] 87:13 **179**/**180**

Table 3.6

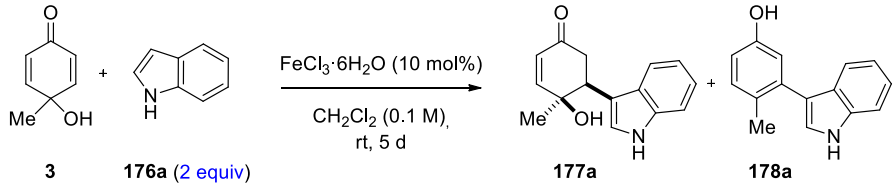
We finally undertook two last experiments concerning the temperature (**Scheme 3.42**) and the amount of equivalents of the indole (**Scheme 3.43**). When the reaction was carried out

at 0 °C instead of at rt, after 3 days the ratio of the FC alkylated versus arylated was similar, but the conversion decreased to a 70% obtaining a 96:4 ratio of **177a** and **178a**. Performing the reaction at room temperature allowed obtaining better results (**Scheme 3.42**).



Scheme 3.42

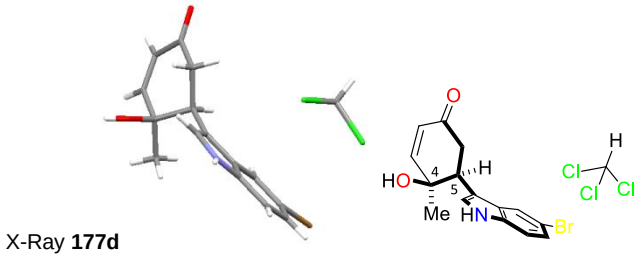
Finally, the used of 2 equiv of indole under the best reaction conditions did not have any effect on the reaction evolution, and a 90:10 ratio of **177a**/**178a** was obtained after 5 days (**Scheme 3.43**).



Scheme 3.43

After all these assays, we conclude that the best reaction conditions to obtain the FC alkylated compound **177a** were the addition of $FeCl_3 \cdot 6H_2O$ (10 mol%) to a CH_2Cl_2 (0.1 M) solution of *p*-quinol **3** (1 equiv) and indole **176a** (1.1 equiv), at room temperature.

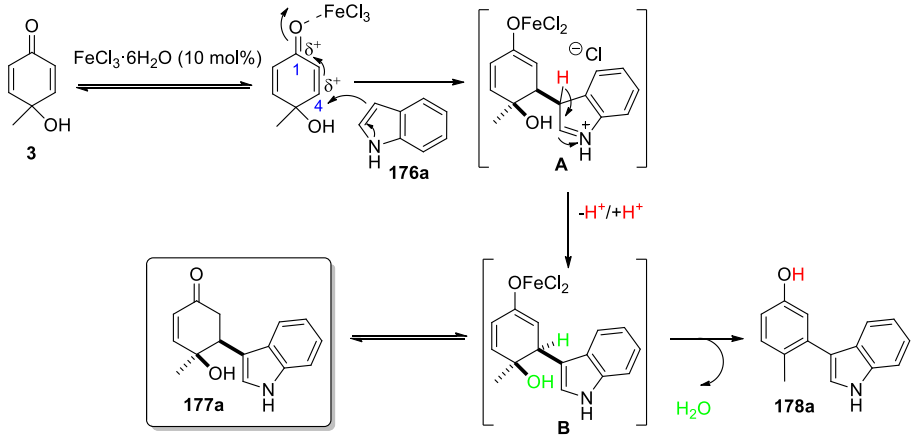
The unequivocal structure of diastereoisomer **177** was confirmed by the X-ray diffraction of **177d**, whose crystalline structure includes a chloroform molecule. The X-ray diffraction evidences the *cis*-relative relationship between the hydroxyl group at C-4 and the indolyl group at C-5 (**Scheme 3.44**).



X-Ray **177d**

Scheme 3.44

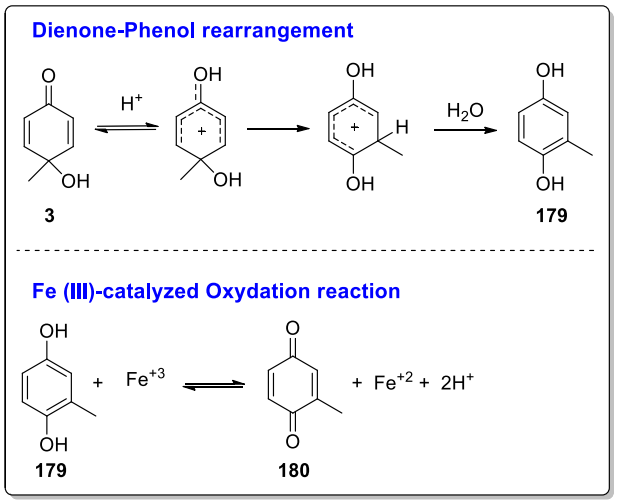
The synthesis of compound **177a** is assumed to proceed via the reaction sequence shown in **Scheme 3.45**. The Lewis acid $FeCl_3 \cdot 6H_2O$ could activated the *p*-quinol, by association with the oxygen atom of the carbonyl group, and then a 1,4-addition of the indole to the conjugate position to generate the iron enolate intermediate **A**, which evolve to iron enolate **B** after recovering the indole aromaticity. After protonation of the iron enolate, **177a** is obtained. The stereochemistry of the overall process could be rationalized according to previous results on conjugate additions on *p*-quinol derivatives,[23] the initial attack of the indole was expected to occur from the less hindered face of **3**, which is the one supporting the OH, with complete π-facial diastereoselectivity. The formation of 3-indolyl-4-methylphenol (10% by GC-MS) **178a** could be a consequence of a deshydratation of intermediate **B**, favoured by the acid medium.



Scheme 3.45

Initial results shown also that 2-methyl-1,4-hydroquinone **179** is formed in the reaction (10-20%, measured by GC-MS in the crude reaction) together with different proportions of the corresponding benzoquinone. The formation of **179** could be a consequence of the acid

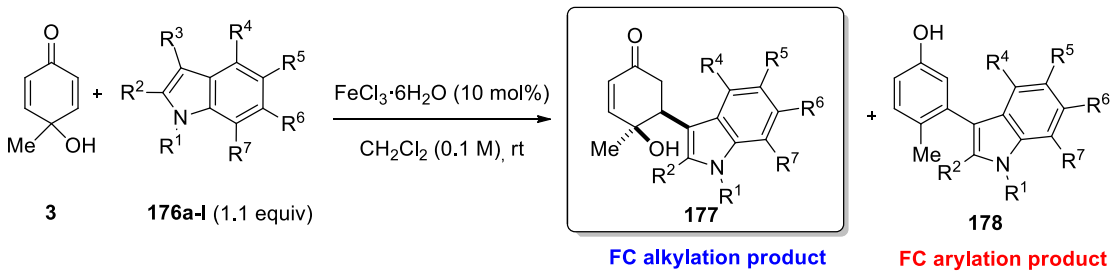
catalyzed dienone–phenol rearrangement[125] of *p*-quinols (**Scheme 3.46**). Moreover, once the hydroquinone **179** is formed, the $FeCl_3$ present in the reaction media can oxidized rapidly **179** to 2-methyl-*p*-benzoquinone **180**, which generated also unproductive iron (II) species and decrease the pH of the reaction mixture due to the generation of HCl. All these transformations of the starting *p*-quinol **3** may be the reason of the low isolated yield of **177a** obtained in certain conditions.



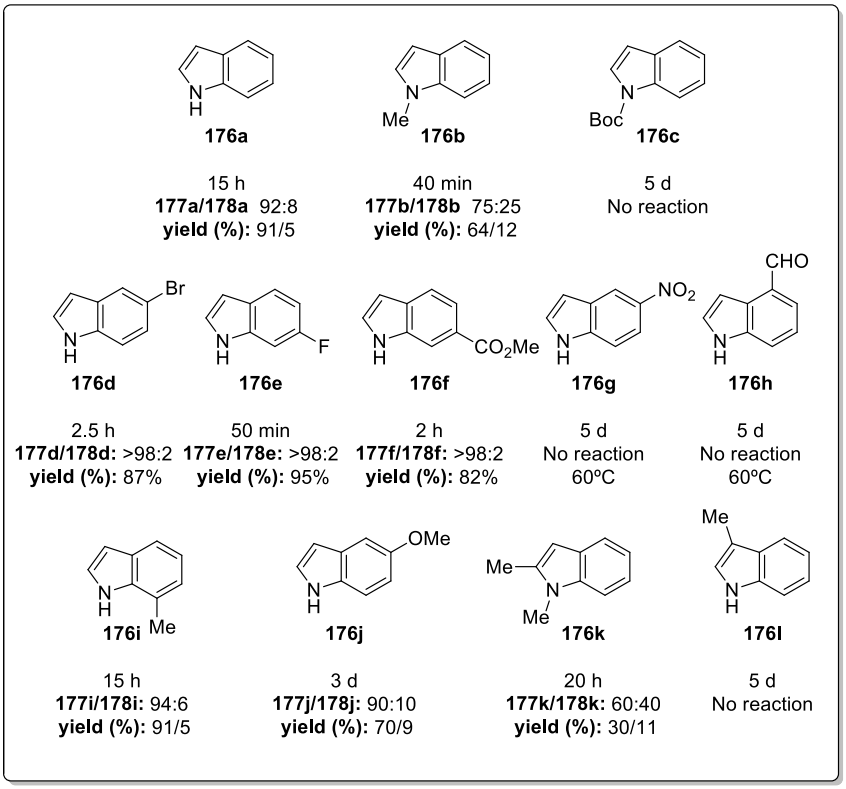
Scheme 3.46

Scope of the conjugate addition of indoles 200a-l to *p*-quinol 3.

With a set of optimized conditions in hands, we next examined the scope of the indole motif in the conjugate addition process (**Scheme 3.47**).



[125] a) Vitullo, V. P.; Grossman, N. *J. Am. Chem. Soc.* **1972**, 94, 3844; b) Chakrabortya, M.; Brzozowskia, C. F.; Novaka, M. *J. Phys. Org. Chem*, **2012**, *25*, 1236.



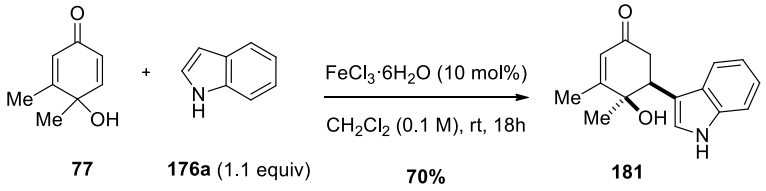
Scheme 3.47

The use of *N*-methyl indole **176b** in CH_2Cl_2 at room temperature, notably accelerates the reaction giving a 75:25 ratio of **177b**:**178b** after 40 min, (64% and 24% yield respectively). No reaction was observed in the case of *N*-*tert*-butylcarbonate (BOC) protected indole **176c**, probably due to the decrease of reactivity of the indole framework towards the Friedel-Craft reaction with *N*-electron withdrawing groups. Indoles bearing electron-withdrawing groups, such as 5-bromo, 6-fluoroindole or 6-methoxycarbonyl (**176d, 176e** and **176f**) smoothly reacted with *p*-quinol **3** and exclusively gave the Friedel-Crafts alkylated products **177d**, **177e** and **177f** in 87%, 95% and 82% yield respectively. Unfortunately, the presence of strong electron withdrawing groups, such as 5-nitro-1H-indole **176g** or 4-carboxaldehyde-1H-indole **176h**, gave unproductive reactions at room temperature or even at higher temperature (60 °C). Electron-rich substituted indoles reacted in all the cases to give the Friedel-Crafts compounds. Thus, reaction of 7-methylindole **176i** with **3** occurred in 15 h to give a mixture 94:6 of **177i/178i** (91% and 5% yield respectively). Reaction with electron rich 5-methoxy indole **176j** was complete after 3 days to afford a 90:10 ratio of **177j/178j** in (70% and 9% yield respectively). Interestingly, methyl substitution at C2 of the indole seems to have no detrimental effect on the reactivity. The reaction of 1,2-dimethylindole **176k** gave a 60:40 ratio

(**177k:178k**) after 20 h (30% and 11% isolated yield respectively). On the contrary, no Friedel Crafts reaction was observed with C-3 substituted indole **176l**.

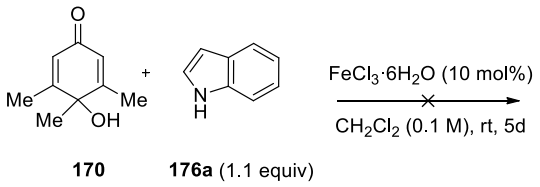
Scope of the conjugate addition of indole 176a to differently substituted *p*-quinols.

The scope of the FC reaction was further explored with other *p*-quinol systems as Michael acceptors. The reaction of substituted 3-methyl-*p*-quinol **77** and indole **176a** under the optimized conditions exclusively afforded the FC alkylated product **181** in 70% isolated yield, as a unique diastereoisomer (**Scheme 3.48**). The preferred attack of the indole on the more electrophilic C-5 conjugated position was expected on the basis of its higher electrophilicty. As in the case of unsubtituted *p*-quinols, the indole attack occurred with complete π-facial diastereoselectivity from the face of the OH group. In this case, the FC arylated product was not observed.



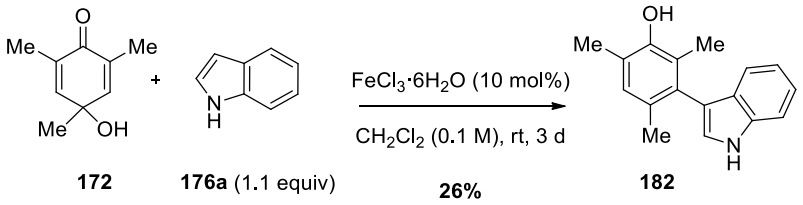
Scheme 3.48

Unfortunately, when the 3,5-dimethyl-*p*-quinol **170** was treated with indole **176a** in the same experimental conditions no reaction takes place (**Scheme 3.49**). The presence of a methyl group at the conjugate position could decrease the electrophicity of the *p*-quinol.



Scheme 3.49

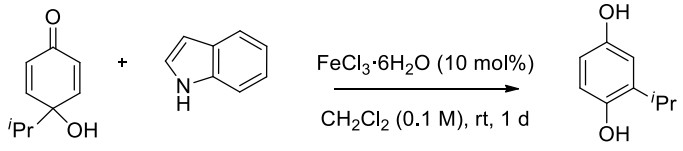
In the case of 2,6-dimethyl-*p*-quinol **172** reaction with indole **176a** gave only the FC arylated compound **182**, although in moderated conventions. The 3-indolyl 2,4,6-trimethylphenol **182** was obtained in a 26% isolated yield after 3 days of reaction (**Scheme 3.50**).



172 **176a** (1.1 equiv) **26%** **182**

Scheme 3.50

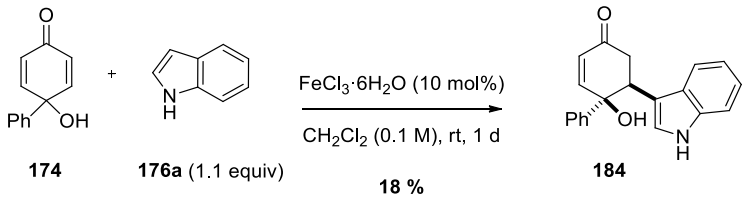
Next, we studied the influence of the substitution at C-4. The reaction seems to be quite sensitive to steric and electronic effects. For instance, more sterically hindered 4-*iso*propyl *p*-quinol **37** did not react with the indol under the optimized reaction conditions, and instead, the dienone-phenol rearrangement was observed in a 50% after 1 day of reaction (**Scheme 3.51**).



37 **176a** (1.1 equiv) **50%** **183**

Scheme 3.51

In the case of 4-phenyl-*p*-quinol **197** the reaction with indol gave a complex mixture from where the FC alkylated compound **208** could be isolated in 18 % yield with complete diastereoselectivity (**Scheme 3.52**). In this case, neither the dienone-phenol rearrangement product nor the FC arylated products were observed in the crude reaction.

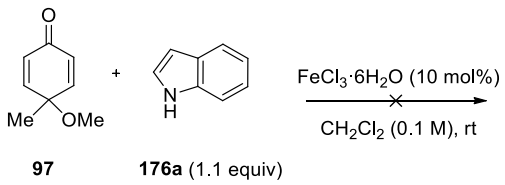


174 **176a** (1.1 equiv) **18 %** **184**

Scheme 3.52

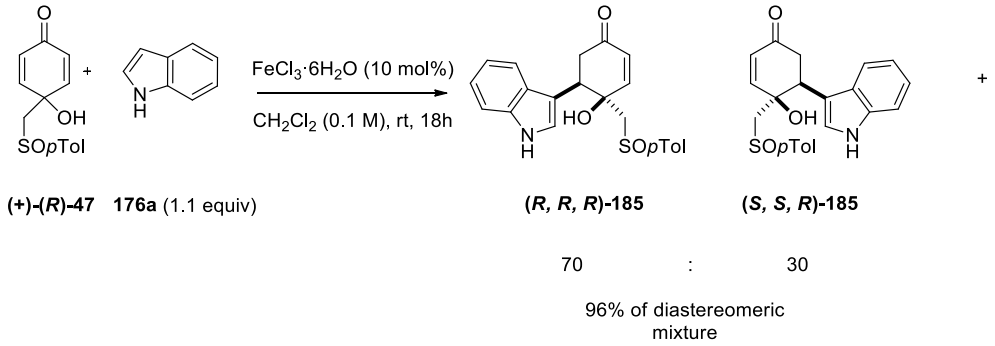
We next evaluated the *p*-quinol **97** with the OH derivatized as a methyl ether. Under the optimized reaction conditions the reaction with indole did not afford any of the FC addition

products (**Scheme 3.53**), showing that the free OH is crucial for both selectivity and reactivity of the process.



Scheme 3.53

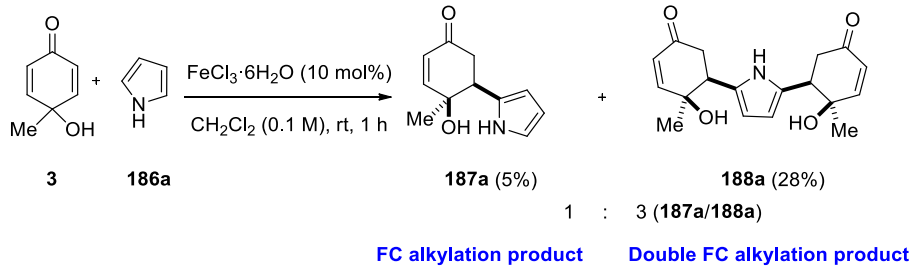
We finally runned the reaction with the enantiopure (+)-*R*-*p*-tolylsulfinylmethyl substituted *p*-quinol **47**. After 18 h, we observed the formation of the FC alkylated compound **185** as a 70:30 diastereomeric mixture in 96% isolated yield of both diastereoisomers **(*R*,*R*,*R*)-185** and **(*S*,*S*,*R*)-185** (**Scheme 3.54**). Based on the experimental results obtained by our research group on the addition reactions of other nucleophiles to (+)-*R*-*p*-tolylsulfinylquinol **47**[23] we assume that the two observed diastereoisomers correspond to the conjugate addition two both prochiral C-3 β-positions, by the face containing the OH group.



Scheme 3.54

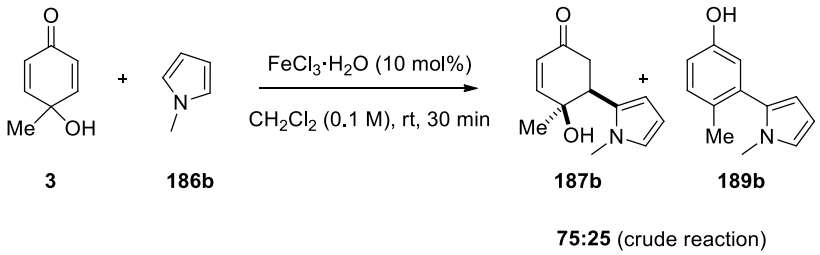
Conjugate addition reactions of π-excedent heteroaromatic derivatives to *p*-quinol 3.

Reactions of *p*-quinol **3** with other heteroaromatic derivatives, such as pyrroles, furans or thiophens, were next explored. As shown in **Scheme 3.55**, pyrrole **186a** was particulary reactive. When *p*-quinol **3** and pyrrole **186a** reacted in the presence of $FeCl_3 \cdot 6H_2O$ (10 mol%) a 1:3 mixture of the mono FC and the bis FC alkylated compounds **187a** and **188a** were obtained in 5% and 28% isolated yield respectively from a complex mixture reaction.



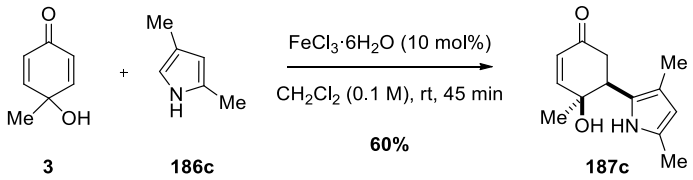
Scheme 3.55

The low conversion observed in this case could be caused due to the polymerization side reaction of pyrrol. When *p*-quinol **3** was treated with *N*-methyl pyrrol **186b**, after 30 min the starting materials were no longer detected and a 75:25 mixture of the FC alkylated and arylated products **187b**:**189b** were observed in the crude reaction. Unfortunately, both compounds resulted unstable on the purification process using flash column chromatography (**Scheme 3.56**).



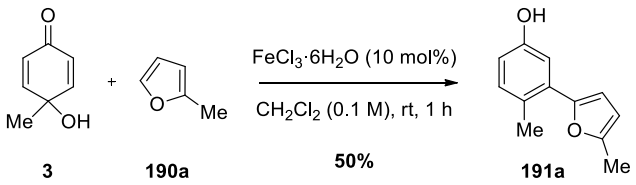
Scheme 3.56

The mono-alkylated FC product could be obtained in good yields in the case of 2,4-dimethylpyrrol **186c**. Thus, under the optimized reaction conditions, pyrrol **186c** and *p*-quinol **3** afforded compound **187c** in 60% isolated yield (**Scheme 3.57**).



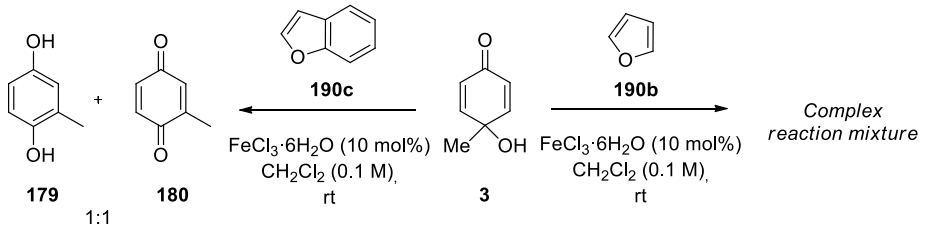
Scheme 3.57

The reaction of *p*-quinol **3** with 2-methyl furan **190a** gave, after 1 hour, the FC arylated compound **191a** with a 50% isolated yield (**Scheme 3.58**).



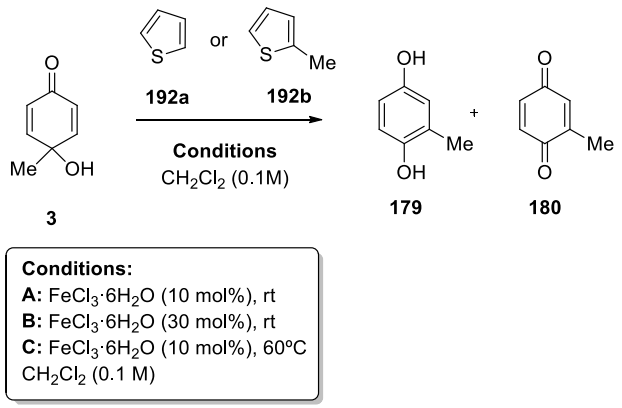
Scheme 3.58

Unfortunately, less reactive furan **190b** or benzofuran **190c** did not react with *p*-quinol **3** obtaining a complex mixture in the case of furan, and a 1:1 mixture of the hydroquinone **179** and the 2-methylbenzoquinone **180** in the second case, together with benzofuran (**Scheme 3.59**).



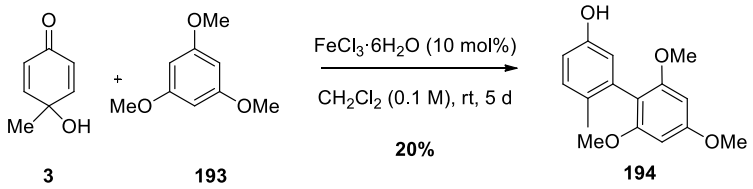
Scheme 3.59

Similar results were obtained in the reaction of *p*-quinol **3** with thiophen **192a** or methylthiophen **192b** using 10 mol% of $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2 (0.1 M) at room temperature. In both cases only hydroquinone **179** and 2-methylbenzoquinone **180** were observed by GC-MS spectroscopy. Attemps to improve the reactivity by increasing the amount of the iron Lewis acid from 10% mol to 30 mol% or raising the reaction temperature to 60°C also failed (**Scheme 3.60**).



Scheme 3.60

The reaction of electron-rich aromatic derivatives such as **193** gave the FC arylation product **194** in 20% yield (**Scheme 3.61**).



Scheme 3.61

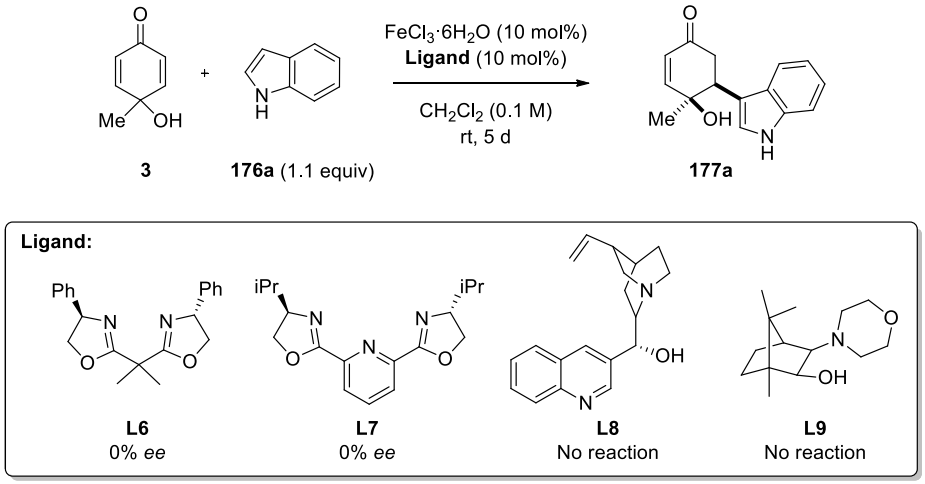
Enantioselective conjugate addition of indoles to p-quinols.

Encouraged by the excellent results obtained in the reaction of indoles with *p*-quinols using 10 mol% of a Fe (III) catalyst ($FeCl_3 \cdot 6H_2O$) as the Lewis acid, we next decided to explore the asymmetric version of the FC reaction using different enantiopure ligands.

The affinity of iron to the nitrogen atom is known since there are really stable complexes such as hemoglobin in the nature. In the literature there are some examples using bisoxazoline ligands as chiral inductors enantioselective iron-catalysed processes.[126,127] Thus, we initiaded our study of the enantioselective FC alkylation of indole **176a** to *p*-quinol **3** catalyzed by $FeCl_3 \cdot 6H_2O$ in the presence of bisoxazolidine **L6** (10 mol%) as the iron ligand. The reaction turned out to be slower than in the absence of this additive, and after 5 days, the FC alkylated compound was obtained in very low conversion and in a 0% *ee*, measured by chiral HPLC (IC-

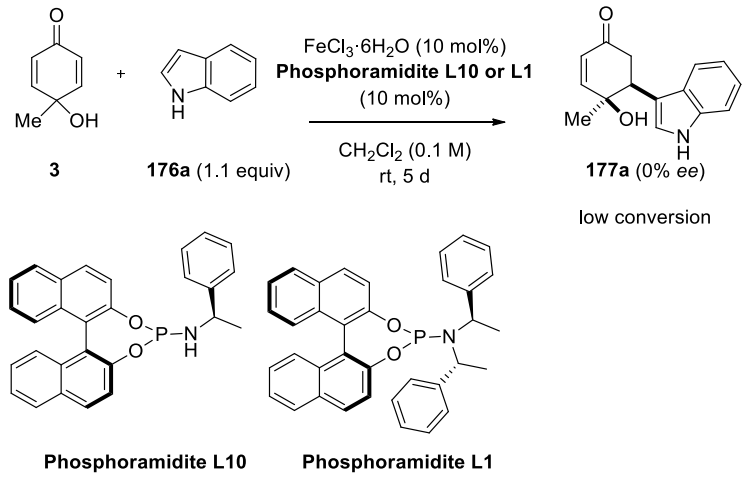
[126] Zhu, S-F.; Cai, Y.; Mao, H-X.; Xie, J-H.; Zhou, Q-L. *Nature Chem.* **2010**, *2*, 546.
[127] Deng, Q-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356.

0.8ml/min-15% ^{i}PrOH-45 min) (**Scheme 3.62**). The use of pybox **L7** as ligand gave similar results in terms of reactivity and enantioselectivity (**Scheme 3.62**). We next decided to use N,O-type ligands, such as Cinchonidine **L8** or isoborneol **L9**, however in these cases, the reaction was completely inhibited (**Scheme 3.62**)



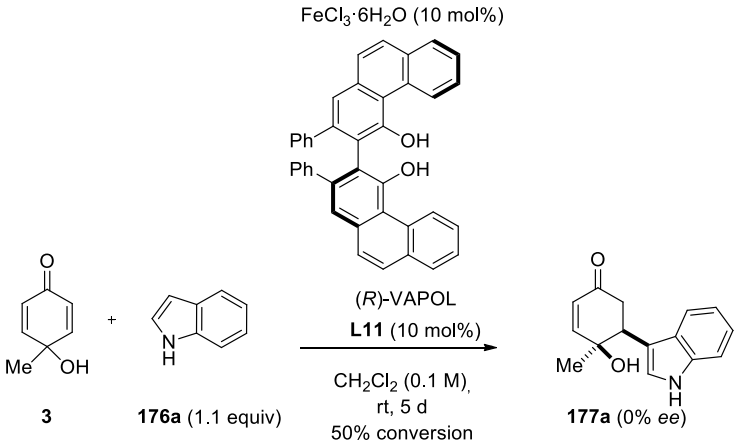
Scheme 3.62

Based on the enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents (R_2Zn) to several 4,4-disubstituted cyclohexadienones using chiral enantiopure phosphoramidite ligands developed by Feringa *et al.,*[22] we decided to use these phosphoramidites as iron (III) ligands in the intermolecular desymmetrization of quinol **3** with indole **176a**. Unfortunately, the conversion of the reaction using phosphoramidite **L10** or **L1** were low and no enantioselectivity was achieved (**Scheme 3.63**).



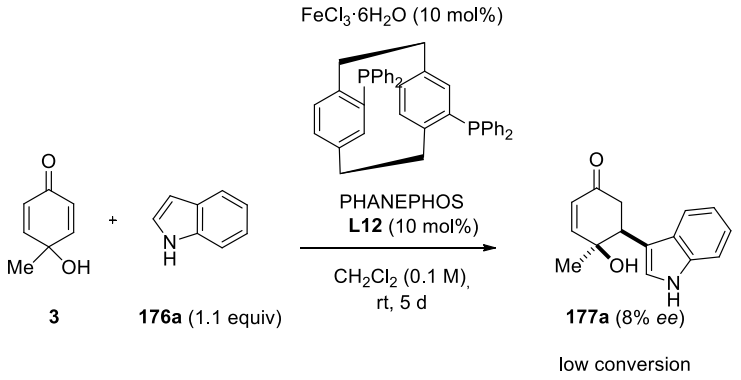
Scheme 3.63

The use of an oxygenated bidentate ligand as *(R)*-VAPOL **L11** gave the FC alkylated product **177a** with a 50% conversion, and 0% of *ee* (**Scheme 3.64**).



Scheme 3.64

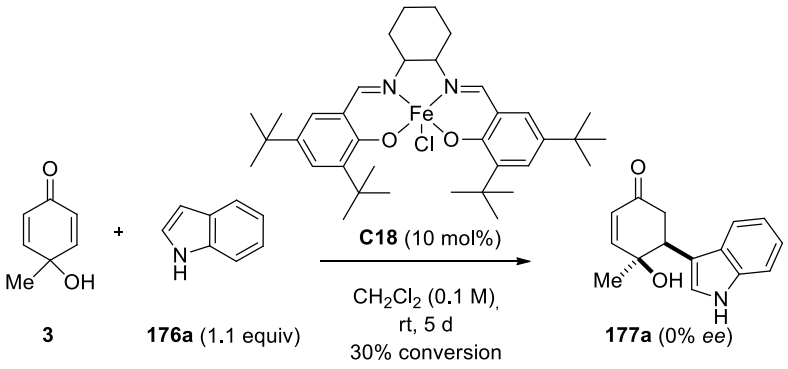
Phanephos bidentate phosphine ligand **L12** gave a 8% *ee* of the FC alkylated compound with a low conversion as well (**Scheme 3.65**).



Scheme 3.65

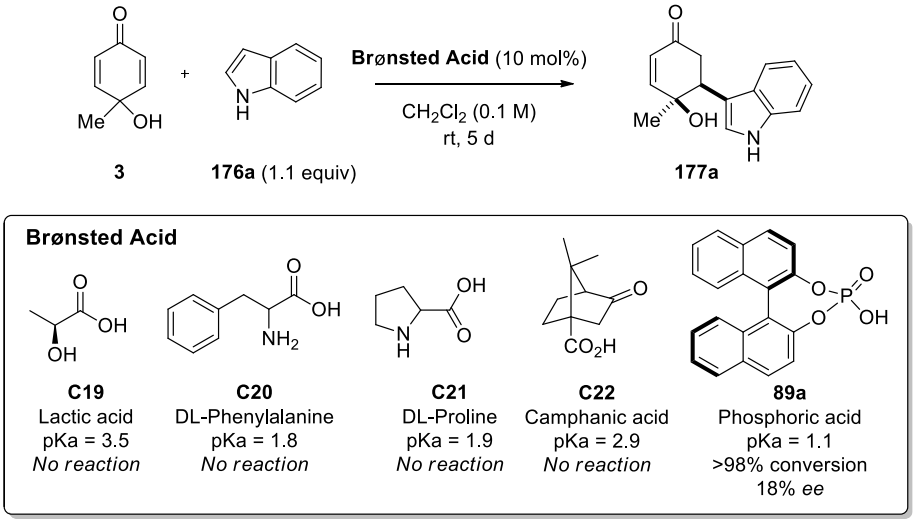
We next explored the use of salen complexes of Fe(III) synthetized by means of the treatment of $FeCl_3$ with the corresponding ligand in MeOH over 16 hours.[128] The reaction of *p*-quinol **3** with indol **176a** using **C18** as catalyst gave a 30% of conversion to the FC alkylated compound, however no enantioselectivy was observed (**Scheme 3.66**).

[128] Bryliakov, K. P.; Talsi, E. P. *Chem. Eur. J.* **2007**, *13*, 8045.



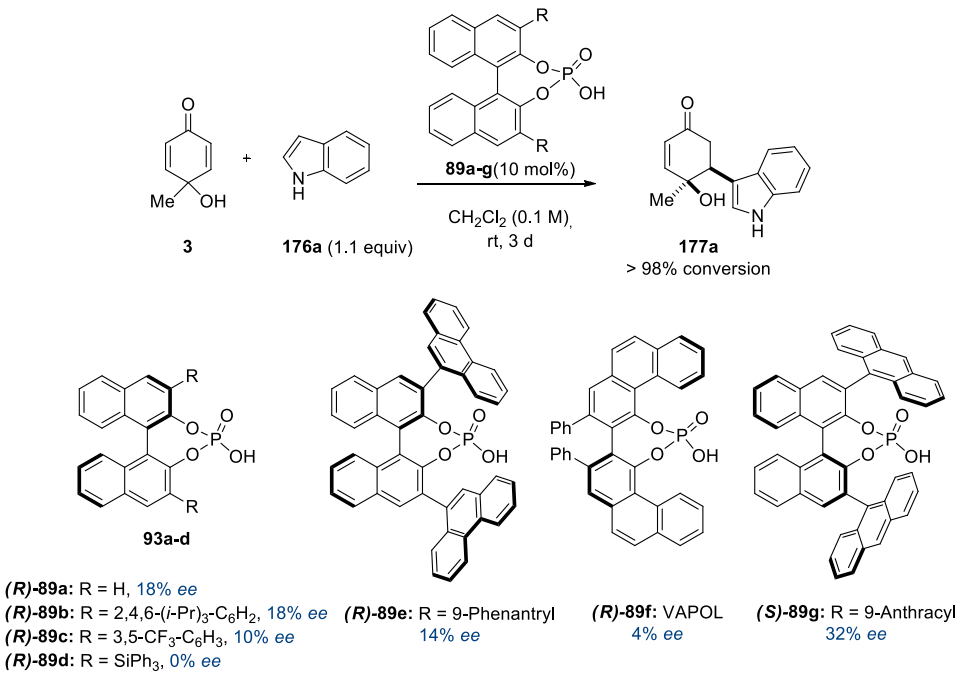
Scheme 3.66

As it has been previously reported in this chapter, the FC reaction of indole **176a** and *p*-quinol **3** took place also in the presence of a Brønsted acid such as the *p*-toluenesulfonic acid (*p*TSA), although in this case the FC arylated compound was the major compound, we decided to check different chiral brønsted acids in order to achieve the desymmetrization of the cyclohexen-2,5-dienone. The use of lactic acid **C19**, the racemic aminoacids phenylalanine **C20** or proline **C21** or the camphanic acid **C22** did not promote any reactivity, recovering the starting materials unaltered (**Scheme 3.67**). Fortunately, the use of the phosphoric acid **89a** derived from BINOL, previously tested in the synthesis of 1,3-dioxol-5-ones from *p*-quinol **3** and aliphatic aldehydes, gave the FC alkylated product with a complete conversion after 5 days and a 18% *ee* (**Scheme 3.67**). The absence of reactivity in all cases excepting with the use of the phosphoric acid may be due to the lower pka of the phosphoric acid, which better activates the carbonyl group of *p*-quinol **3** to favor the addition of indole **176a**.



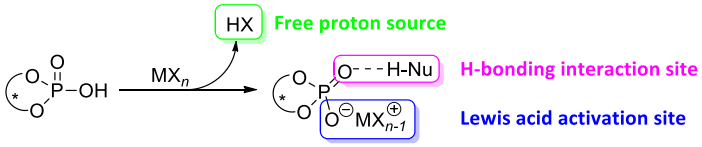
Scheme 3.67

With this result, we started to evaluate different enantiopure phosphoric acids. The results are summarized in **Scheme 3.68**. In all cases the FC alkylated compound **177a** was obtained in a > 98% of conversion. When bulky 2,4,6-(^{i}Pr)$_3$-C$_6$H$_2$ substituted phosphoric acid **89b** was used a 18% *ee* was obtained. The use of less hindered 3,5-CF$_3$-C$_6$H$_3$ substituted phosphoric acid **89c** gave a 10% *ee*. Triphenylsilane substituted phosphoric acid **89d** gave no enantioselective induction. 9-Phenantryl derivative **89e** afforded only a 14% *ee*. We next tested the phosphoric acid **89f** derived from VAPOL ligand but only 4% *ee* was observed.The best result was obtained in the case of *(S)*-9-anthracyl derivative **89g**, where a 32% *ee* was observed in the HPLC analysis of the purified product **177a**.



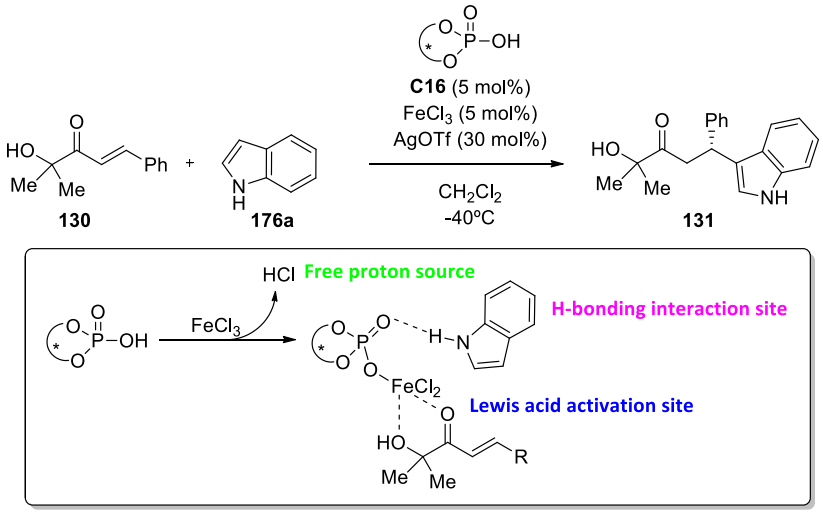
Scheme 3.68

In order to improve these results, we tested the use of binary catalysts constituted by a metal and a phosphoric acid. The success of this methodology relays on a cooperative catalytic system, with a Lewis acid site for activating the electrophile and a base site for activating the nucleophile through a hydrogen-bonding interaction. The free proton source accelerates the proton transfer from the nucleophile moiety (indole or electron-rich aromatic ring) to newly generated enolate (**Scheme 3.69**).



Scheme 3.69

As an example of this binary catalyst cooperation, the group of Huang[108] used a binary catalyst using Fe (III) as metallic source in the alkylation of indoles with β-Aryl α'-Hydroxy enones **130** affording the FC alkylated product **131** (**Scheme 3.70**). The authors proposed that the Fe(III)-phosphate could associate to both starting materials. The hydroxyl and the carbonyl group of β-Aryl α'-Hydroxy enone would coordinate to the Lewis acid activation site and the indole core would establish hydrogen bond with the Lewis basic activation site. The HCl delivered in the formation of the binary catalyst would protonate the resulting enolate once the FC alkylation takes place. Silver salts such as AgOTf showed to improve the enantioselective excess of this reaction.

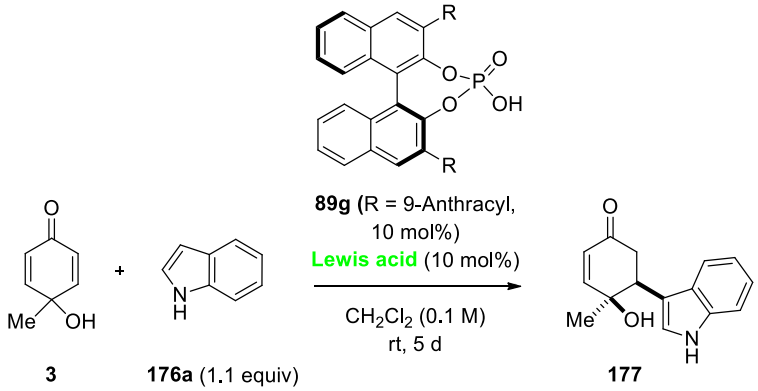


Scheme 3.70

Cheng *et al.*[109] described the 1,2- or 1,4-addition of *N*-protected indoles with β,γ-unsaturated α-keto esters using a binary catalyst constituted of a In(III) salt and a phosphoric acid. Depending on the metal component used in the reaction, the regioselectivity of 1,2- or

1,4-addition was achieved. This group has also developed a binary system constituted by MgF_2 as metal in the reactions of phenols with β,γ-unsaturated α-keto esters.[129]

With this background we envisaged the use of a chiral binary catalyst in the enantioselective FC reaction of indole **176a** with *p*-quinol **3**. We initially tested the combination of the best phosphoric acid derivative **89g** (10 mol%) with $FeCl_3{\cdot}6H_2O$ (10 mol%). The reaction of indole **176a** and *p*-quinol **3** using this catalyst system, afforded excellent conversion but a racemic mixture of the FC alkylated compound **177a** was observed by HPLC (**Table 3.7, entry 2**). Using the same reaction conditions but adding AgOTf (30 mol%) as an additive a 10% *ee* was obtained (**Table 3.7, entry 3**). The combination of $InBr_3$ and **89g** gave the same results in terms of conversion but the enantioselectivity was nule (**Table 3.7, entry 4**). Using MgF_2 and **89g** the *ee* slightly increased to 20% but with a lower conversion (less than 50%) (**Table 3.7, entry 5**).



Entry	Lewis acid	Time	Conversion to **177a** (%)	*ee* (%)[a]
1	-	3 d	>98%	32
2	$FeCl_3{\cdot}6H_2O$	2 d	>98%	0
3	$FeCl_3{\cdot}6H_2O$/AgOTf	2 d	>98%	10
4	$InBr_3$	2 d	>98%	0
5	MgF_2	2 d	<50%	20

[a] Enantiomeric ratio measured by HPLC analysis (IC-0.8ml/min-15% ^{i}PrOH-45 min)

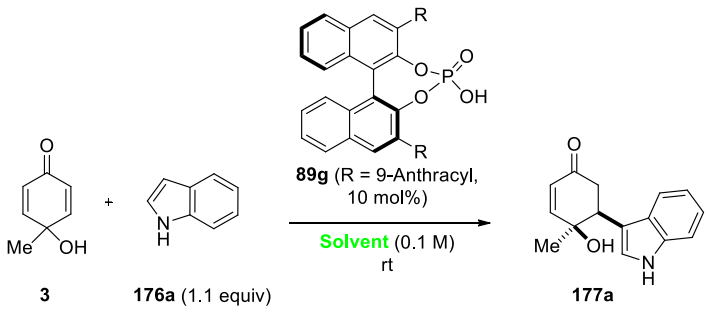
Table 3.7

Considering that the use of phosphoric acid **89g** gave better results (**Table 3.7, entry 1**) than in combination with the Lewis acids tested, we followed our study screening different solvents, temperatures and concentration in order to improve the *ee* values.

[129] Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, J-P. *Org. Lett.* **2010**, *12*, 1096.

We first studied the effect of the solvent in the FC reaction of indole **176a** with quinol **3** (**Table 3.8**), catalyzed by phosphoric acid **89g**. In all cases, the reaction time was controlled by the disappearance of the starting material by GC-MS.

As previously described, the use of CH_2Cl_2 gave, after 3 days, a total conversion and a 32% of *ee* (**Table 3.8, entry 1**). The use of dichloroethane (DCE) or the less polar solvent toluene gave similar conversions and enantioselectivities (**Table 3.8, entries 2 and 3**). The reaction with ether solvents such as diethyl ether (**Table 3.8, entry 4**) or tetrahydrofuran (THF) (**Table 3.8, entry 5**), gave lower conversions (75 and 60% respectively) but an increasement of the enantiomeric excess was measured in the case of THF (50% *ee*). The use of a more polar aprotic acetonitrile (CH_3CN) as solvent (**Table 3.8, entry 6**), gave after 6 days a 80% conversion to the FC compound **177a** in a 50% isolated yield and a 50% *ee*. Different polar protic solvents were also tested. The use of ethanol (**Table 3.8, entry 7**) or *tert*-buthanol (**Table 3.8, entry 8**) gave similar conversions (< 50% in both cases, after 6) and enantioselectivities (26% and 28% *ee*). When *iso*-propanol was used, a 70% of conversion and 38% *ee* were observed after 6 days of reaction (**Table 3.8, entry 9**). Addition of molecular shieves is known to increase the enantiomeric excess in some organocatalytic reactions. However, the addition of 4 Å molecular shieves in the reaction media inhibited completely the reaction (**Table 3.8, entry 10**). Therefore, we later added a catalytic amount of water (10 mol%) to the reaction of indole **176a** and quinol **3** in CH_3CN (0.1 M) at rt using the phosphoric acid **89g** as catalyst. Under these conditions, the enantiomeric excess increased to 60% although with a 50% of conversion after 6 days (**Table 3.8, entry 11**). The decreasement of the solubility of the starting materials in the reaction media could be the origin of the low conversion. Running the reaction with CH_3CN at 0.5 M, reaction time notably decreased to 2 day, with a complete conversion and 58% *ee*. When higher concentrations were used, the starting materials precipitated in the reaction media. Therefore, we decided to continue our screening study with CH_3CN (0.5 M).



3 **176a** (1.1 equiv) **177a**

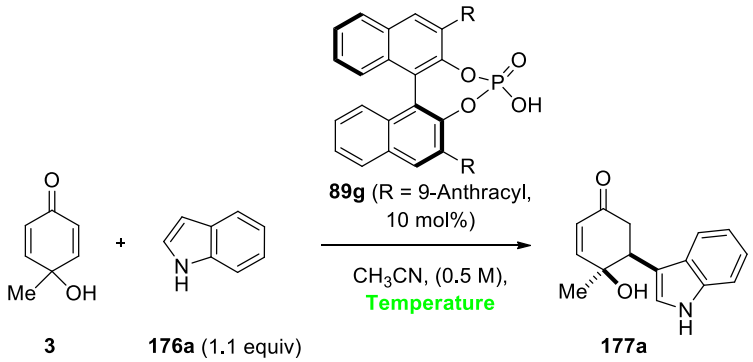
Entry	Solvent	Time	Conversion to **177a** (%)	*ee* (%)[a]
1	CH_2Cl_2	3 d	>98%	32
2	DCE	3 d	>98%	38
3	Toluene	2 d	>98%	28
4	Et_2O	6 d	75%	32
5	THF	6 d	60%	50
6	CH_3CN	6 d	>80% (50% yield)	50
7	EtOH	6 d	< 50%	26
8	^{t}BuOH	6 d	< 50%	28
9	^{i}PrOH	6 d	70%	38
10	^{i}PrOH[b]	6 d	-	-
11	CH_3CN[c]	6 d	50%	60
12	CH_3CN[d]	2 d	>98%	58

[a] Enantiomeric ratio measured by HPLC analysis (IC-0.8ml/min-15% ^{i}PrOH-45 min); [b] Use of activated MS 4Å; [c] H_2O (10 mol% was added); [d] 0.5 M

Table 3.8

We next explored the influence of the temperature in the enantioselectivity. Since the freezing point of acetonitrile is around -45 °C we only checked two different temperatures below room temperature (**Table 3.9**).

When the temperature was dropped to -20 °C the enantioselectivity improves notably (72% *ee*), with a 80% of conversion after 6 days (**Table 3.9, entry 2**). At -40 °C similar enantioselectivities were observed, but only a 40% of conversion was obtained after 6 days of reaction (**Table 3.9, entry 3**).

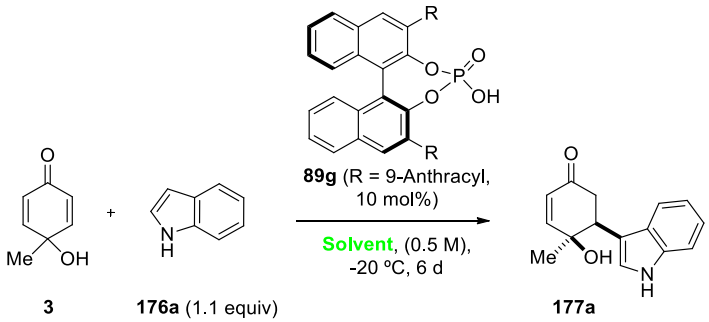


Entry	Temperature	Time	Conversion to **177a** (%)	*ee* (%)[a]
1	rt	2 d	> 98%	58
2	-20 °C	6 d	80% (72% yield)	72
3	-40 °C	6 d	40%	70

[a] Enantiomeric ratio measured by HPLC analysis (IC-0.8ml/min-15% ^{i}PrOH-45 min).

Table 3.9

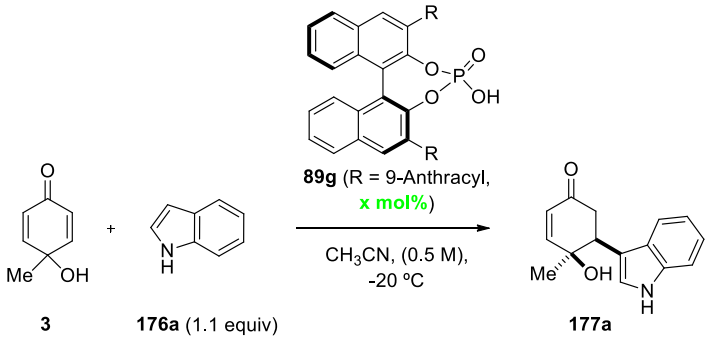
Some other polar aprotic solvents were tested under these new optimized conditions. In particular, acetone, DMF, AcOEt and dioxane were tested (**Table 3.10**). Unfortunately, none of them gave better results than CH_3CN. Using acetone or DMF as solvents in 0.5 M, no conversion to the FC alkylated product was observed in the crude reaction (**Table 3.10, entries 1 and 2**). Ethyl acetate gave a 50% *ee* of compound **201a** with a 50% of conversion (**Table 3.10, entry 3**) and dioxane gave similar results in terms of enantioselectivity (44% *ee*) but with higher conversion (**Table 3.10, entry 4**).



Entry	Solvent	Conversion to **177a** (%)	*ee* (%)
1	Acetone	-	-
2	DMF	-	-
3	AcOEt	50%	50
4	Dioxane	80%	44

Table 3.10

Regarding the catalyst loading, and increasement from 10 mol% to 15 mol% afforded a complete conversion after 9 days, although the *ee* decreased to 60% (**Table 3.11, entry 2**). When 5 mol% was used, the conversion dropped to 30% even after 15 days of reaction and a 60% *ee* was observed (**Table 3.11, entry 3**). Variations in the addition order of the reagents did not produced significant changes, as it was expected for the reaction times.



Entry	x mol%	Time	Conversion to **177a** (%)	*ee* (%)[a]
1	10	6 d	80% (72% yield)	72
2	15	9 d	> 98%	60
3	5	15 d	30%	60

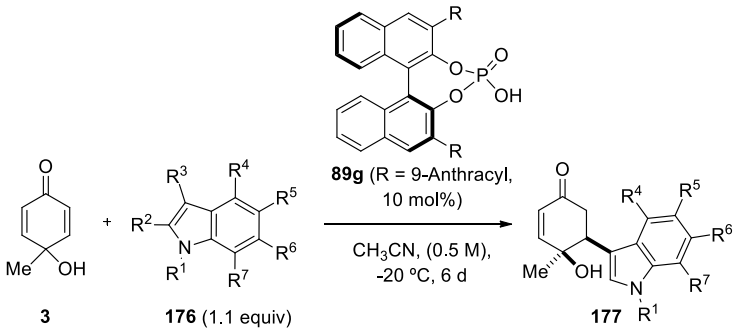
[a] Enantiomeric ratio measured by HPLC analysis (IC-0.8ml/min-15% ^{i}PrOH-45 min)

Table 3.11

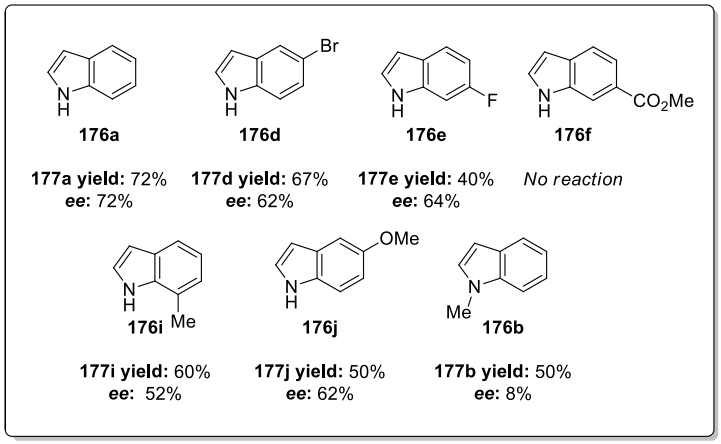
Scope of the conjugated addition of indoles 176 to *p*-quinol 3 catalyzed by phosphoric acid 89g.

Once stablished the optimized reaction conditions for the enantioselective FC addition of indole **176a** to *p*-quinol **3** using phosphoric acid **89g** as catalyst, we studied the scope of this reaction with other different indoles (

Scheme 3.71).



Scheme 3.71



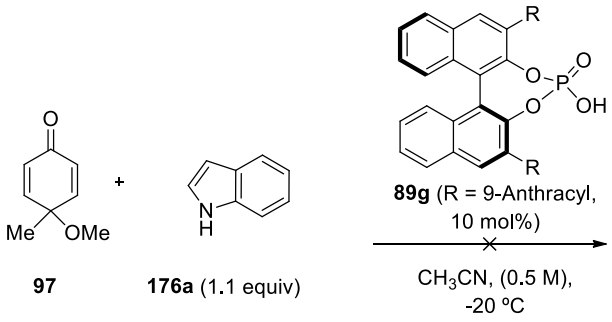
The reaction tolerated indoles with electron withdrawing substituents and electron donating substituents. Electron withdrawing substituents (**176d:** R^5 = Br and **176e:** R^6 = F) gave similar results without significant erosion of the enantioselectivity. Thus, compounds **177d** and **177e** could be isolated in a 67% and 40% yield and a 62% and 64% *ee* respectively. Unfortunately, more electron withdrawing methyl ester carboxylate substituted indole **176f** did not afford the FC alkylated product. Electron donating substituted indoles (**176i:** R^7 = Me and **176j:** R^5 = OMe) gave the corresponding FC alkylated compound in good isolated yields and similar *ee* (**177i:** 60%, 52% *ee*; **177j:** 50%, 62% *ee*) (

Scheme 3.71).

To our surprise, the reaction with *N*-methyl indol **176b** gave the FC alkylated product **177b** in 50% isolated yield but as a racemic mixture (

Scheme 3.71). This absence of enantioselectivity indicated that the N-H group of the indole has an essential role in the desymmetrization process.

The *O*-methyl substituted quinol **97** did not give any reaction with indole **176a** in the phosphoric acid **89g** catalyzed reaction (**Scheme 3.72**). This lack of reactivity was also observed in the Lewis acid ($FeCl_3 \cdot 6H_2O$) catalyzed reaction. These results indicated that the hydrogen atom of the hydroxyl group of the *p*-quinol **3** is playing a crucial role in the outcome of the reaction in both racemic and asymmetric version.

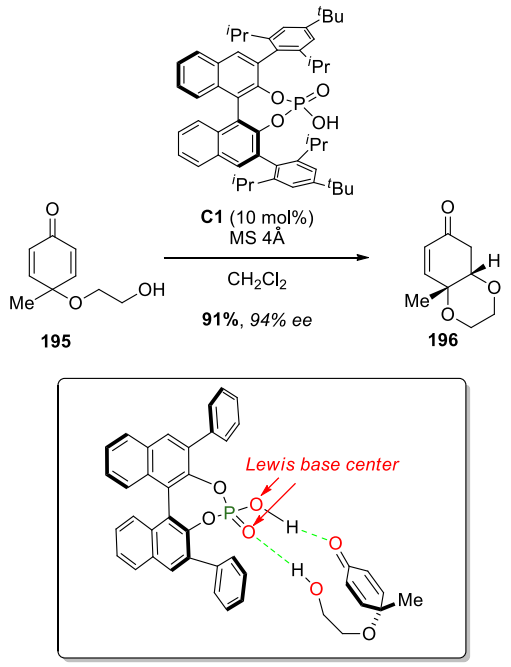


Scheme 3.72

To rationalize the chiral induction mechanism of the asymmetric 1,4 conjugated addition of indoles to the 2,5-cyclohexadienone moeity using a chiral phosphoric acid as catalyst, we have to consider the following facts:

a) The reaction is inhibited when *p*-quinol is *O*-methyl substituted, and the *ee* falls when the indole is *N*-methyl substituted. The main differences between the *p*-quinol **3** and the *O*-methyl *p*-quinol **97** and the indole **176a** and *N*-methyl indole **176b** are in their ability to form hydrogen bonds which is possible in the case of free OH and free NH derivatives **3** and **176a**, and lost for *O*-methyl *p*-quinol **97** and *N*-methyl indol **176b** derivatives.
b) Moreover, when the phosphoric acid catalyzed the reaction of free OH *p*-quinol **3** and free N-H indole **176a** is performed in the presence of molecular shieves, again there is an inhibition of the reactivity. Therefore, water must have an essential role in the reactive transition state.

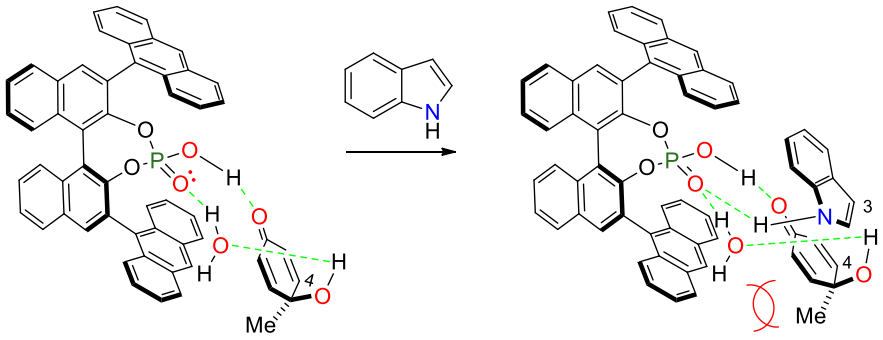
At this point, it is interesting to consider the model of activation proposed by You[42] for the asymmetric intramolecular 1,4-addition of *O*-(2-(hydroxyethyl)-*p*-quinols **195** catalyzed by chiral phosphoric acid **C1** affording the conjugate addition products **196** (**Scheme 3.73**). In this paper, the authors suggested a double site coordination by means of two different hydrogen bonding: one between the free OH of the phosphoric acid and the Lewis base oxygen of the carbonyl group of *p*-quinol, and the second, between the free OH of *O*-(2-(hydroxyethyl)-*p*-quinol **231** and the lewis base (P=O) site of the phosphoric acid (see **Scheme 3.73**).



Scheme 3.73

In our case, considering that water has a dramatic effect on the reactivity, we propose a similar double activation model, in where a H_2O molecule is tethering the double hydrogen bond type of coordination with the phosphoric acid and the *p*-quinol **3**. As it is shown in ***TS 1*** of **Figure 3.5**, the H_2O could be associated by an hydrogen bond to the free OH of the *p*-quinol, and at the same time, could stablish a hydrogen bond with the oxygen Lewis base site of the phosphoric acid (P=O). A second hydrogen bond between the free OH of phosphoric acid and the carbonyl oxygen of *p*-quinol could be activating the system.

The X-Ray structure of **177d** shows a *syn* relationship between the indole core from **176d** and the OH group from *p*-quinol **3**. The lack of enantiomeric exccess when indole is *N*-methyl substituted **176b** could be suggesting the presence of a third hydrogen bond in the latter transition state that could be assisting the asymmetric FC alkylation by the less hindered face of the cyclohexadienenone moiety which is the face containing the hydroxyl group (***TS 2***, **Figure 3.5**).



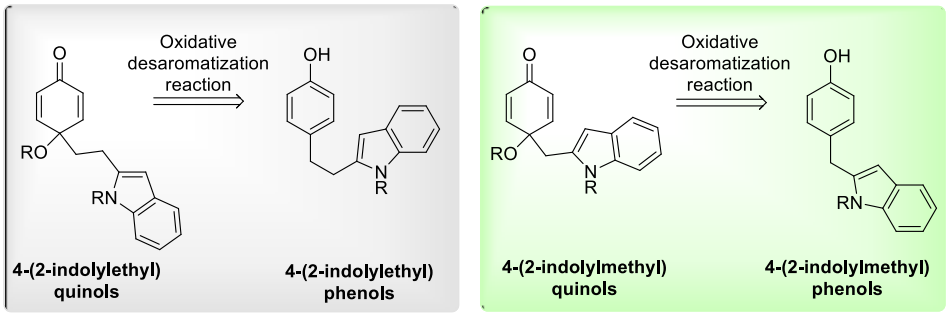
TS 1 ***TS 2***

Figure 3.5

3.2.2. Intramolecular Friedel-Crafts reaction of 4-(2-indolylalkyl)quinols.

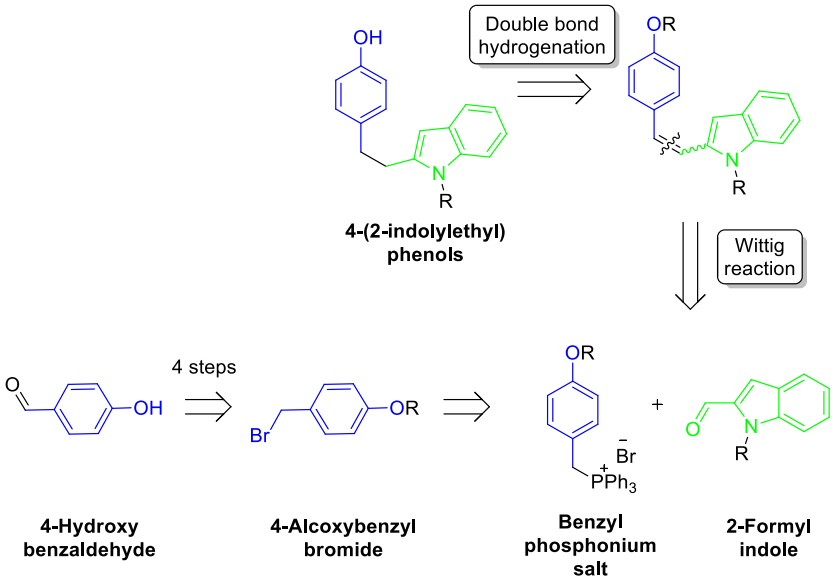
Synthesis of starting materials.

The study of the intramolecular version of the Friedel-Crafts reaction was initiated with the synthesis of the *p*-quinol precursors. In particular the synthesis of the 4-(2-indolyl)ethyl and 4-(2-indolyl)methyl *p*-quinols could be accessible from the corresponding 4-(2-indolylalkyl)phenols by an oxidative dearomatization reaction (**Scheme 3.74**).



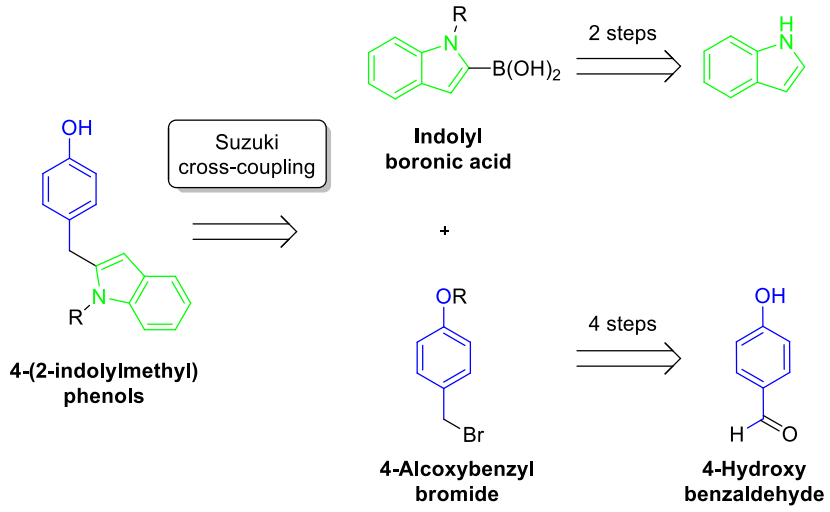
Scheme 3.74

The indolyl ethyl phenol skeleton could be formed from 2-formyl indole, through a Wittig olefination with the phosphonium salt, followed by double bond hydrogenation. Benzyl phosphonium salt is accessible from 4-alcoxybenzyl bromide which could be fashioned from commercially available 4-hydroxybenzaldehyde in 4 steps following known protocols (**Scheme 3.75**).



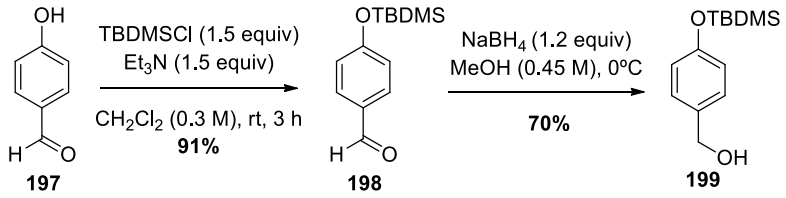
Scheme 3.75

The strategy for the construction of indolyl methyl phenol is shown in **Scheme 3.76**. The synthesis of 4-(2-indolyl)methyl phenols could be achieved through a Suzuki cross-coupling reaction between indolyl boronic acid and *p*-alcoxybenzylic bromide. The indolyl boronic acid could be readily accessible by standard borylation protocols from simple 1H-indole, while the 4-alcoxybenzylbromide will be synthetized as in the above indolylethyl serie, following known protocols.



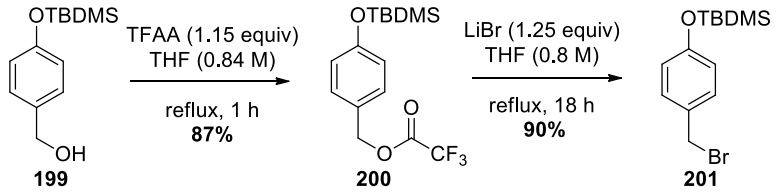
Scheme 3.76

We started the preparation of *N*-methyl-indolyl ethyl phenol **209** with the synthesis of *p*-alcoxy benzyl bromide **201** from *p*-hydroxy benzaldehyde **197**. Protection of the hydroxyl group of **197** as ^{t}buthyldimethylsilyl ether under the standard conditions (TBDMSCl, Et_3N) gave compound **198** in 91% yield (**Scheme 3.77**).[130] Reduction of the aldehyde **198** using $NaBH_4$ as the reducing agent in a MeOH[131] solution at 0°C gave bencylic alcohol **199** in a 70% yield, that could be used in the following step without further purification (**Scheme 3.77**).



Scheme 3.77

Exchange of the hydroxy group of **199** to bromide atom, was achieved by means of a trifluoroacetate intermediate **200**.[131] Thus, reaction of bencylic alcohol **199** with trifluoroacetic anhydride in a THF solution at 80°C for 1 hour afforded the trifluoroacetate derivative **200** in a 87% yield (**Scheme 3.78**), that was directly converted to the bencylic bromide by reaction with LiBr in THF at 80°C. In this manner, benzyl bromide **201** was obtained in a 90% yield,[131] and could be used without further purification in the following transformation to the corresponding phosphonium salt (**Scheme 3.78**).

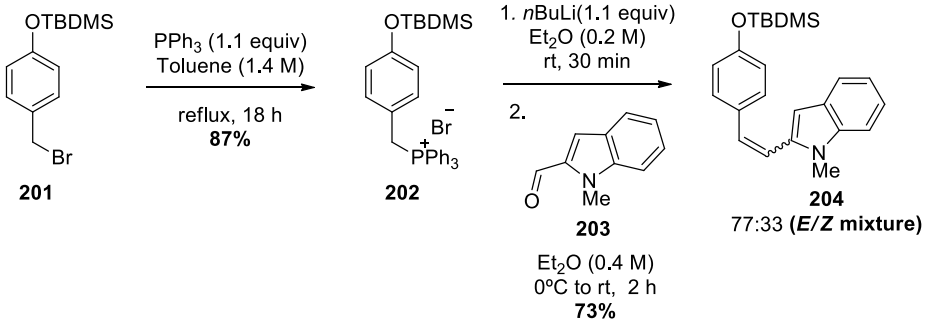


Scheme 3.78

Phosphonium salt **202** was prepared by reaction between PPh_3 and the benzyl bromide **201** (**Scheme 3.79**),[132] in a 87% yield after filtratrion from the reaction crude. The Wittig reaction of the phosphonium salt **202** was initially achieved with commercially available *N*-methyl protected indole-2-carboxaldehyde **203** using *n*BuLi as base for the formation of the

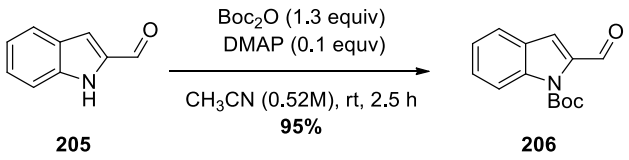
[130] Kwong, C. K-W.; Huang, R.; Zhang M.; Shi, M.; Toy, P. H. *Chem. Eur. J.* **2007**, *13*, 2369.
[131] Nuñez, S. A.; Yeung, K.; Fox, N. S.; Phillips, S. T. *J. Org. Chem*. **2011**, *76*, 10099.
[132] Sella, E.; Shabat D. *Org. Biomol. Chem.* **2013**, *11*, 5074.

phosphorous ylide.[133] After 2 hours, a 77:33 mixture of **204** as a *E/Z* mixture of isomers, was obtained in a 73% isolated yield. Both stereoisomers were further used in the alkene hydrogenation step (**Scheme 3.79**).



Scheme 3.79

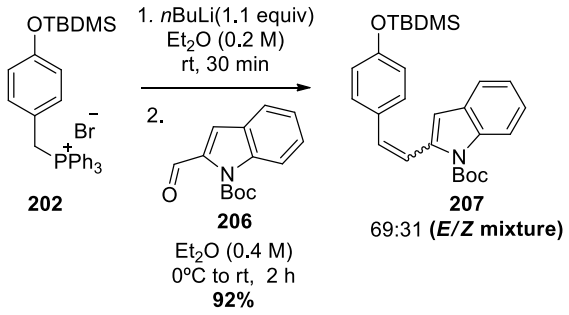
Taking into consideration that the N-H group of the indol seems to play an important role in the phosphoric acid catalyzed enantioselective FC alkylation of *p*-quinol with indoles, we also synthetized the *N*-Boc protected derivative **210**. Compound **210** could be prepared from *N*-Boc-2-formyl-indole **206** that could give direct acces to the desired free N-H derivatives, and the benzyl phosphonium salt **202**. *N*-Boc-2-formyl-indole **206** was readly available in 95% yield from indole-2-carboxaldehyde **205** by treatment with ^{t}buthyldicarbonate and a catalytic amount of DMAP in CH_3CN at room temperature (**Scheme 3.80**).[134]



Scheme 3.80

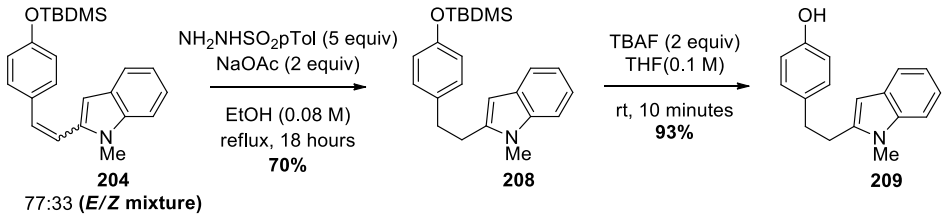
The Wittig reaction[133] between the phosphonium salt **202** and the *N*-Boc indole-2-carbaldehyde **206**, using *n*BuLi as base, gave **207** as a 69:31 mixture of the isomers ***E/Z*** in a 92% isolated yield (**Scheme 3.81**).

[133] Rojas-Martín, J.; Veguillas, M.; Ribagorda, M.; Carreño, M. C. *Org. Lett.* **2013**, *15*, 5686.
[134] Özüduru, G.; Schubach, T.; Boysen, M. *Org. Lett.* **2012**, *14*, 4990.



Scheme 3.81

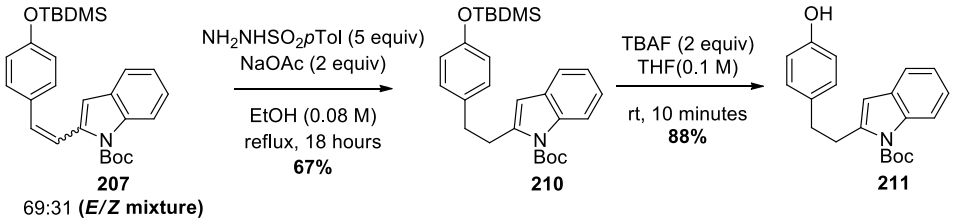
Since catalytic hydrogenation had been proved to be an efficient and convenient process for the conversion of stilbenes to dihydrostilbenes, we initially tested two heterogeneous catalytic hydrogenations using H_2 in combination with Pd/C or Rh/C. Unfortunately, in both cases, the desired saturated compound **208** was obtained together with variable quantities of starting material. Reduction of conjugated double bond could be efficiently performed by reaction with NH_2NHTs and NaOAc in reflux of EtOH under nitrogen atmosphere.[135] Following this methodology, compound **208** was obtained in 70% yield after purification by flash column chromatography (**Scheme 3.82**). Final deprotection of the silyloxy group[136] with tetrabuthylamonium fluoride (TBAF) gave phenol **209** in 93% isolated yield (**Scheme 3.82**).



Scheme 3.82

Similarly, the alkene reduction of **207** with NH_2NHTs, gave a 67% isolated yield of **210** after purification (**Scheme 3.83**). Deprotection of the TBS group using TBAF as fluorinated agent afforded a 88% yield of 4-(indolylethyl)phenol **211** (**Scheme 3.83**).

[135] (a) Lin J.; Zhang W.; Jiang N.; Niu Z.; Bao K.; Zhang L.; Liu D.; Pan C.; Yao X. *J. Nat. Prod.* **2008,** *71,* 1938; (b) Kanekar Y.; Basha K.; Duche S.; Gupte R.; Kapat A. *Eur. J. Med. Chem.* **2013**, *67*, 454.
[136] Corey E. J.; Venkateswarlu A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.



Scheme 3.83

The linear synthesis of the *N*-methyl derivative **209** was achieved in eight steps with a total yield of 21%, five steps to obtain the phosphonium salt **202** and three steps to achieve the desired phenol **209** (**Figure 3.6**). The synthesis of the *N*-Boc derivative **211** has a 22% overall yield, after five steps to obtain the phosphonium salt **202**, one step to obtain the indole-2-carboxaldehyde **206** and three steps to achieve the desired phenol **211** (**Figure 3.6**).

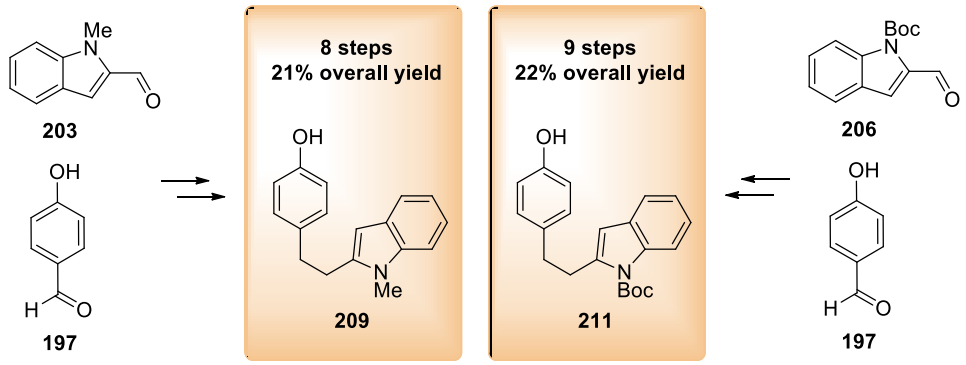
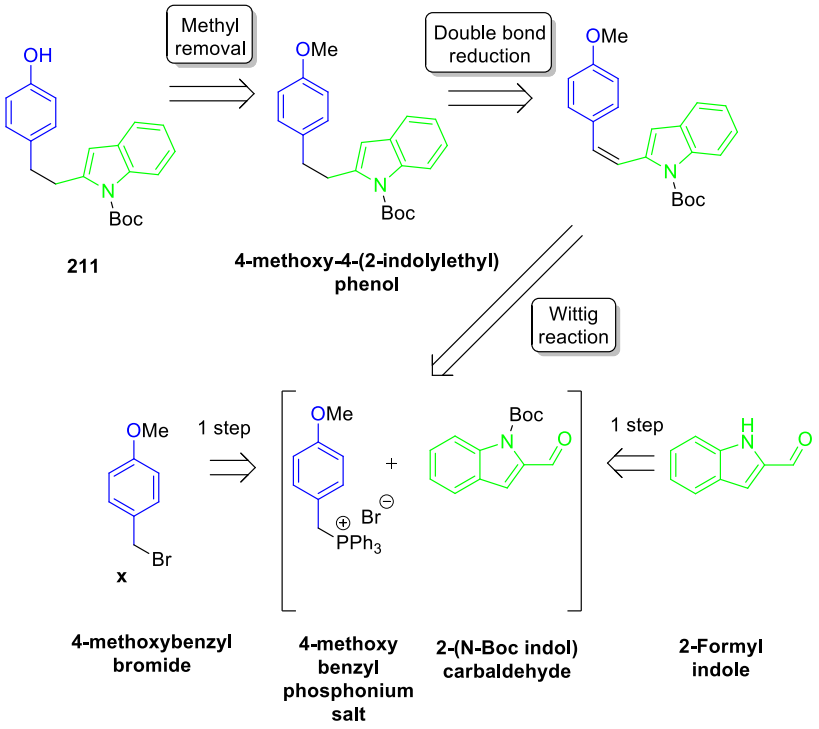


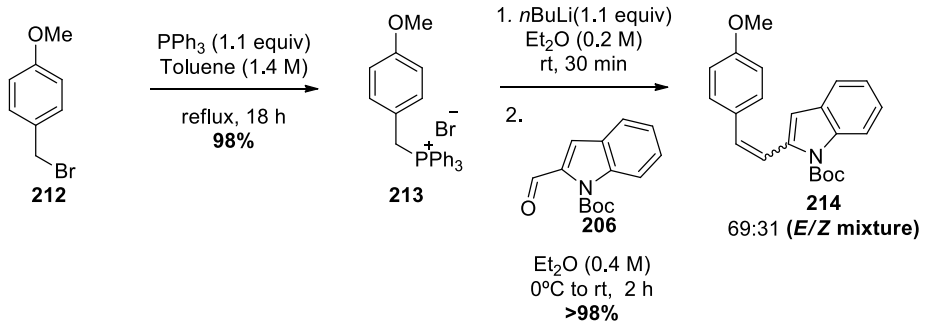
Figure 3.6

The synthesis of 4-(2-indolylethyl)phenol could be also achieved in five steps from commercially available 4-methoxybenzyl bromide and the 2-(*N*-Boc indol)carboxaldehyde following the synthetic plan described in **Scheme 3.84**. The final step would be the methyl removal affording the 4-(2-indolyl)-ethylphenol **211**.



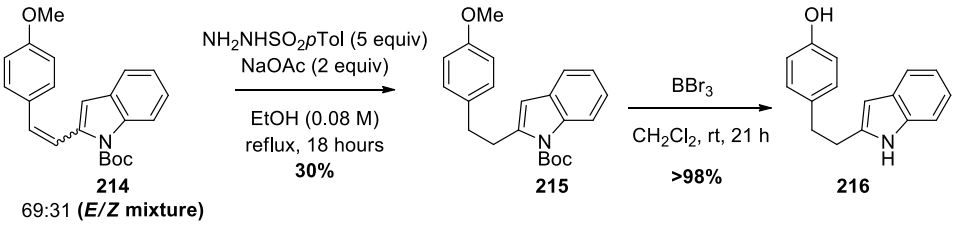
Scheme 3.84

The phosphonium salt **213** was synthetized[132] from commercially available 4-methoxybenzyl bromide **212** and PPh_3, in a 98% yield (**Scheme 3.85**). The Wittig reaction between phosphonium salt **213** and *N*-Boc protected indole-2-carboxaldehyde **206**,[133] using *n*BuLi as base, gave *N*-Boc vinyl indole **214** in a 69:31 mixture of isomers *E/Z* in quantitive yield (**Scheme 3.85**).



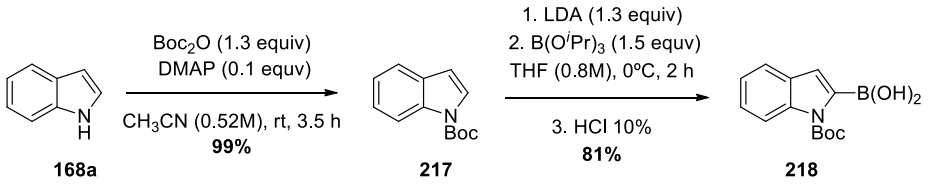
Scheme 3.85

Reduction of alkene **214**[135] with $TsNHNH_2$ gave compound **215** in 30% isolated yield (**Scheme 3.86**). Deprotection of the methyl ether group with BBr_3[137] resulted in the deprotection of both methoxy and *N*-Boc groups in a quantitive manner affording derivative **216** (**Scheme 3.86**).



Scheme 3.86

We started the synthesis of 4-(2-indolylmethyl)phenol **220** following the retrosynthetic plan shown in **Scheme 3.76**. We started with the synthesis of boronic acid **218**.[138] Protection of commercially available 1H-indole **168a** with ^{t}buthyl dicarbonate[134] gave *N*-Boc indole **217** in 99% yield (**Scheme 3.87**). *Ortho*-metallation of *N*-Boc indole **217** with LDA was followed by the addition of $B(O^iPr)_3$ to form the corresponding ester, that after the acidic work up gave the desired boronic acid **218** in a 81% overall yield (**Scheme 3.87**). Although boronic acid **218** was obtained enough pure to be used without further purification, it should be mentioned that all the attempts to purify boronic acid **218** by flash column chromatography or crystallization ended with product decomposition, so it was used without further purification.

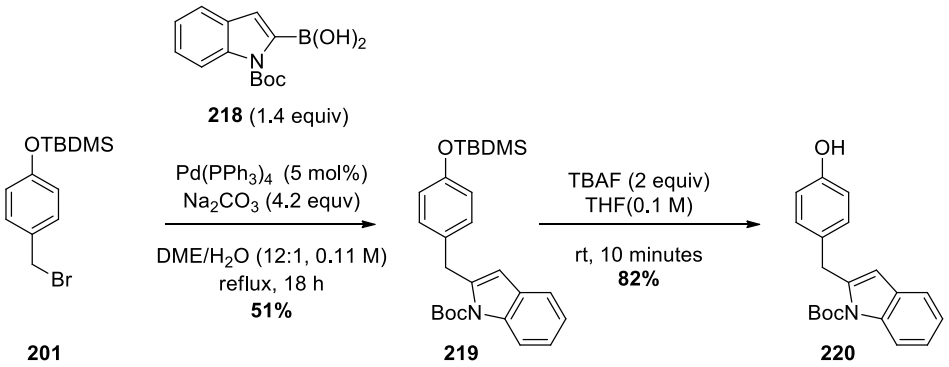


Scheme 3.87

Suzuki cross coupling[139] between aryl bromide **201** and borylated indole **218**, using $Pd(PPh_3)_4$ as catalyst, Na_2CO_3 as base in a 12:1 mixture of DME:H_2O gave, after 18 hours at reflux, compound **219** in 51% yield after flash column chromatography (**Scheme 3.88**).

[137] Teplý, F.; Stará, I. G.; Starý, I.; Kollárovic, A.; Lustinec, D.; Krausová, Z.; Saman, D.; Fiedler, P. *Eur. J. Org. Chem.* **2007**, 4244.
[138] Vázquez, E.; Davies, I. W.; Payack,J. F. *J. Org. Chem*. **2002**, *67*, 7551.
[139] Kearney, A. M.; Landry-Bayle, A.; Gomez, L. *Tet. Lett*. **2010**, *51*, 2281.

Removal of the sililoxy protecting group was performed using TBAF in a THF solution at room temperature. Compound **220** was obtained in 82% yield after flash column purification (**Scheme 3.88**).



Scheme 3.88

Derivative **220** was obtained in a convergent synthesis of 8 steps and 17% overall yield from commercially available 1H-indole **168a** and 4-hydroxybenzaldehyde **197** (**Figure 3.7**).

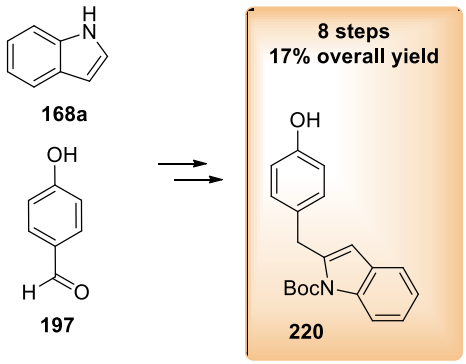


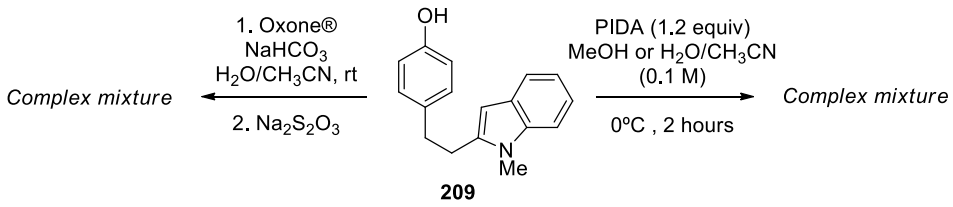
Figure 3.7

Synthesis of p-quinol derivatives and their behavior in the FC reaction.

Once the 4-indolylalkylphenols were prepared we next studied their conversion to the corresponding *p*-quinols.

Reactivity of 4-(2-(1-methyl-1H-indol-2-yl)ethyl)phenol 209 in oxidative dearomatization and FC reactions.

We initially treat the *N*-methylindolylethyl phenol **209** under the standard oxidative conditions using hypervalent iodine species, such as PIDA or PIFA, using MeOH or H_2O as solvent. Unfortunately, in all cases a complex mixture was observed in the ^{1}H-NMR of the reaction crude, which could be attributed to a side oxidation reaction of the electron rich indole core (**Scheme 3.89**). Treatment of electron rich indoles with hypervalent iodine species are reported to promote the oxidative cleavage of the C2-C3 indole bond.[140] Following the methodology described in our group for the synthesis of *p*-quinols from *p*-alkylphenols we treated the starting phenol **209** with Oxone®/$NaHCO_3$ obtaining a complex mixture (**Scheme 3.89**).



Scheme 3.89

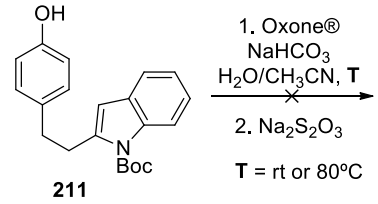
To tackle this issue, reaction was studied with the *N*-Boc protected derivative **211**.

Reactivity of 4-(2-(1-*tert*-butylcarboxylate-indol-2-yl)ethyl)phenol 211 in oxidative dearomatization and FC reactions.

Once the synthesis of the phenol bearing an indole *N*-Boc protected **211** was optimized, we started the study of the reactivity of this singular phenol.

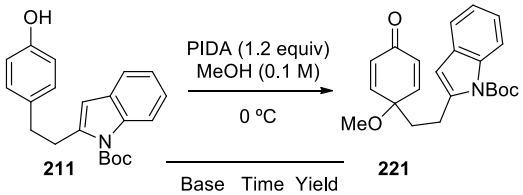
[140] (a) Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc*. **1951**, *73*, 2641–2647. (b) Mentel, M.; Breinbauer, R. *Curr. Org. Chem.* **2007**, *11*, 159–176.

When **211** reacted under the conditions for the synthesis of *p*-quinols from *p*-alkyl phenols using Oxone®/$NaHCO_3$ described by our research group,[36] the starting material was recovered unaltered at rt and at 80ºC (**Scheme 3.90**).



Scheme 3.90

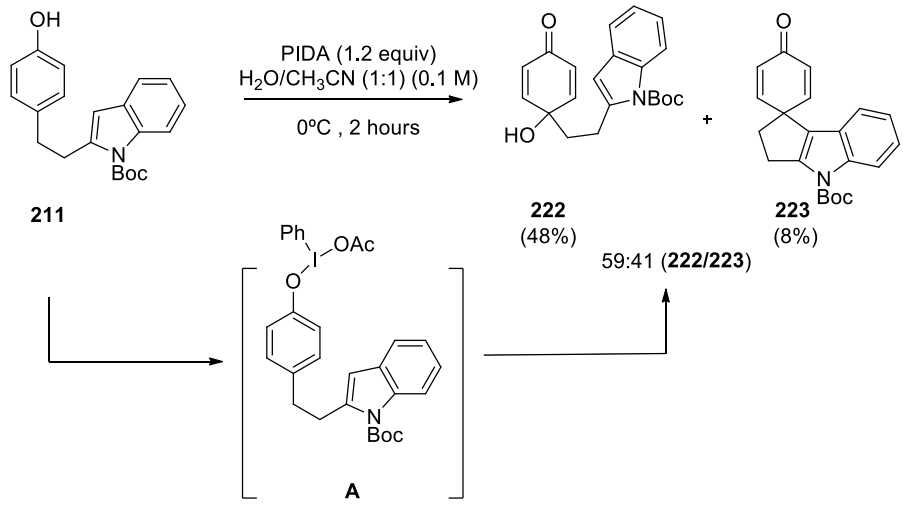
Thus, we decided to try with different hypervalent iodine reagents. When **211** was treated with 1.2 equiv of PIDA in MeOH (0.1 M) in the presence of K_2CO_3 (2 equiv) at 0°C, the methyl ether *p*-quinol **221** was obtained in 39% isolated yield after purification (**Scheme 3.91**). Running the reaction in the absence of the base, the yield of **221** increased to 46%.



Base	Time	Yield
K_2CO_3	3 h	39%
-	2 h	46%

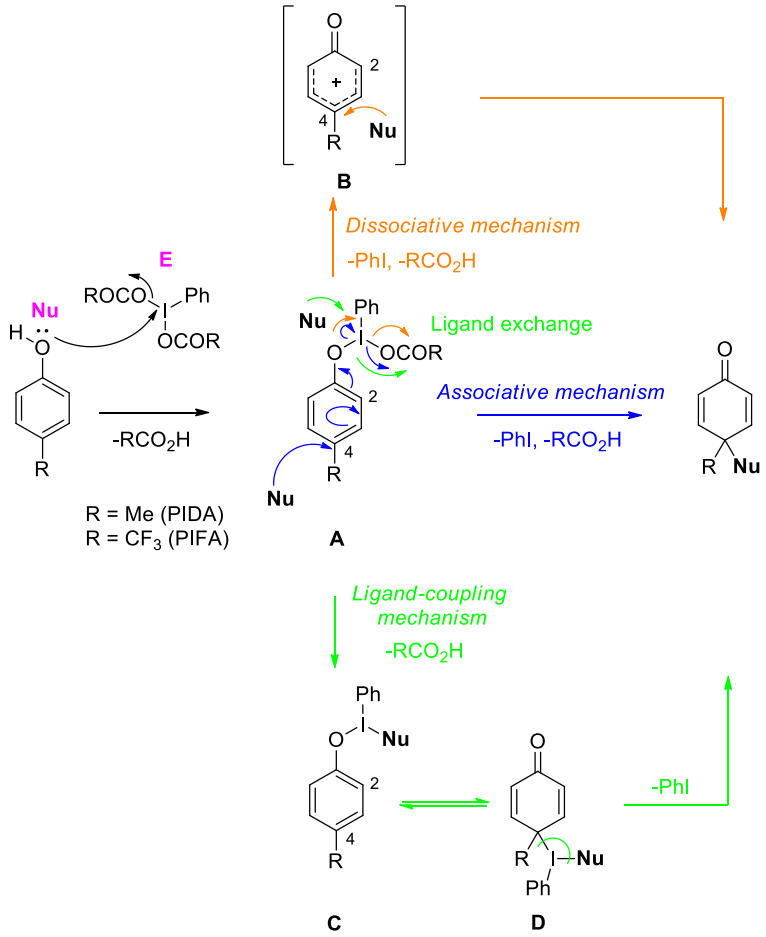
Scheme 3.91

When the reaction solvent was changed from MeOH to H_2O/CH_3CN (1:1) a 59:41 mixture of *p*-quinol **222** and the spirocycle **223** was observed by ^{1}H-NMR spectroscopy. After purification, *p*-quinol **222** was obtained in 48% yield whereas only a 8% yield was achieved of the spirocycle **223** (**Scheme 3.92**).



Scheme 3.92

The oxidative dearomatization mechanism of *p*-alkylphenols using electrophilic hypervalent iodine reagents is not well known. As it has been reported in Chapter 2, there are three possible pathways which could depend on the solvent (polarity, ability of coordination,…) or the regiochemistry and electronic properties of the substituents in the starting *p*-alkylphenol.[32i] As it is shown in **Scheme 3.93**, all the possible mechanisms start by the replacement of one of the $^{-}$OCOR ligands of the iodine specie (III) by the OH group of the phenol, affording **intermediate A**. The ability of iodine (III) species to reduce to iodine (I) species is considered the motrice force of this oxidative dearomatization process. The dissociative mechanism affords the phenoxenium cation (**intermediate B**) which could be attack for a nucleophile. In the associative bimolecular mechanism, the departure of the iodine (I) specie and the attack of the nucleophile happen in a concertate manner, affording directly the desired product. Finally, when the nucleophile replaces a second molecule of $^{-}$OCOR ligand in **intermediate A**, the resulting phenoxy-iodine (III) specie (**intermediate C**) can transform into its 2,5-cyclohexadienyl tautomer (**intermediate D**) in which the nucleophile and the 2,5-cyclohexadienyl substituents on the iodine (III) can couple deplacing the iodine (I) specie as iodobenzene by a reductive elimination.

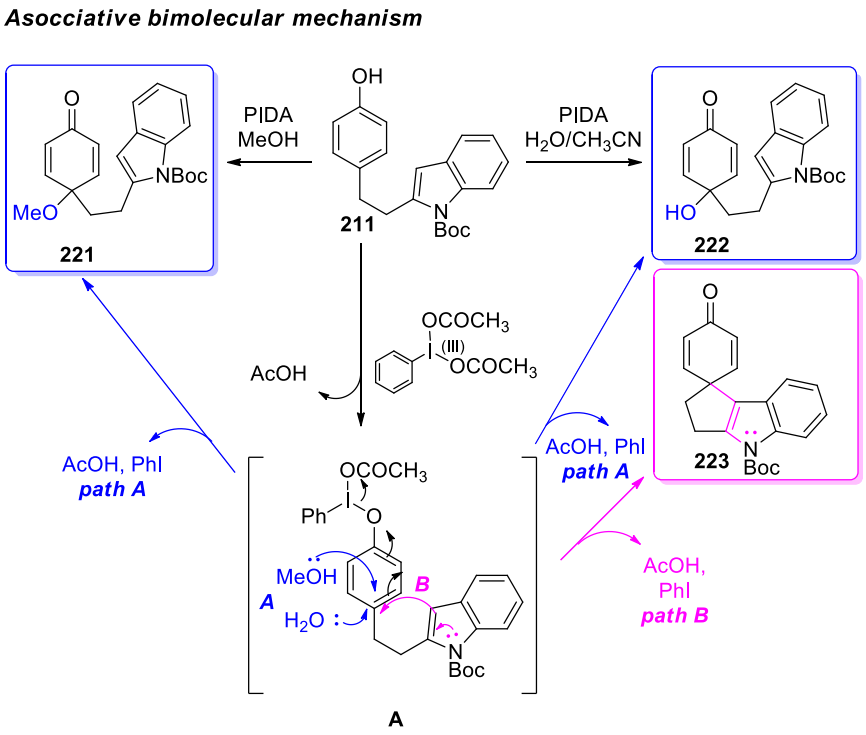


Scheme 3.93

The synthesis of the *p*-quinol derivatives **221** and **222** and the spirocycle **223** could be explain as depicted in **Scheme 3.94**. We consider one of the three mechanisms described above (the associative bimolecular mechanism) in order to facilitate the scheme.

Initially, phenol **211** reacts with a hypervalent iodine reagent, such as PIDA, to generate **intermediate A**. The concertated nucleophilic addition of the solvent and the departure of the iodine (I) specie (iodobenzene) gave *p*-quinol **221** (when MeOH is used) or **222** (when H_2O/CH_3CN is used). Such transformations rely on the electrophilic character of the hypervalent iodine center which conceptually imposes to the hydroxyl group of the phenol to replace, in this case, an acetate ligand on the iodine. This fact switches to phenols from being nucleophiles to becoming electrophiles. This "phenolic umpolung", also more generally first referred to as "aromatic ring umpolung" ,[33] then enables attack of nucleophiles at the *ortho*- or *para*-carbon centers (in this case to the *para*-carbon) of the starting phenol thus oxidatively activated. The formation of the spirocycle **223** could be explained by an intramolecular Friedel

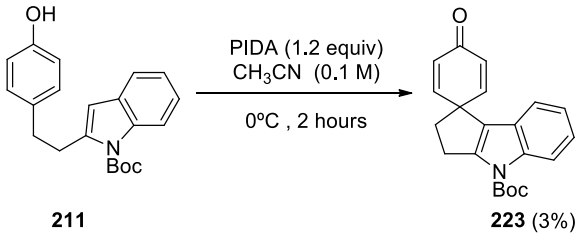
Crafts alkylation of indole framework to the **intermediate A** in competence with the nucleophilic addition of the solvent (MeOH or H_2O) (**Scheme 3.94**).



Scheme 3.94

In this case, using both MeOH and the equimolecular mixture of H_2O and CH_3CN, only the *para*-carbon attack is observed. In the case of using nucleophilic solvents such as MeOH the *O*-methyl protected quinol **221** was exclusively observed. The use of a 1:1 mixture of H_2O (as a nucleophilic solvent) and CH_3CN (as a non-nucleophilic solvent, used to better dissolve the starting material) gave the expected *p*-quinol **222** in competence with the spirocycle **223**, as the result of the nucleophilic attack of C-3 of indole to the *para* position of the phenol.

Attempt to perform the reaction of **211** with PIDA in CH_3CN, as a non nucleophilic solvent to promote the formation of spirocycle **223**, gave only a 3% isolated yield of **223** from a complex reaction mixture (**Scheme 3.95**).



211 **223** (3%)

Scheme 3.95

Reactivity of *tert*-butyl 2-(4-hydroxybenzyl)-1H-indole-1-carboxylate 220 in oxidative dearomatization and FC reactions.

In order to study the synthesis of new tetracyclic structures with two 6-member rings and two 5-member rings (see **Figure 3.8**) we decided to study the behavior of phenol **220** (with a doubly aromatic methylene) in reactions of oxidative dearomatization.

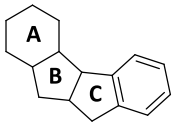
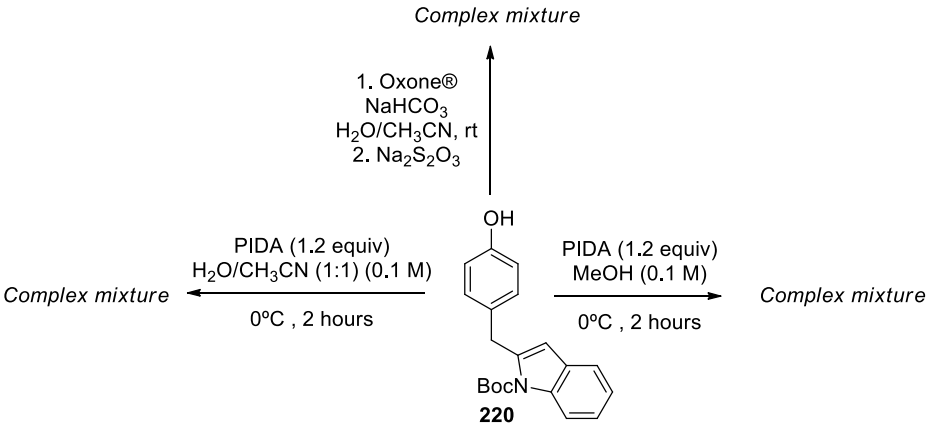


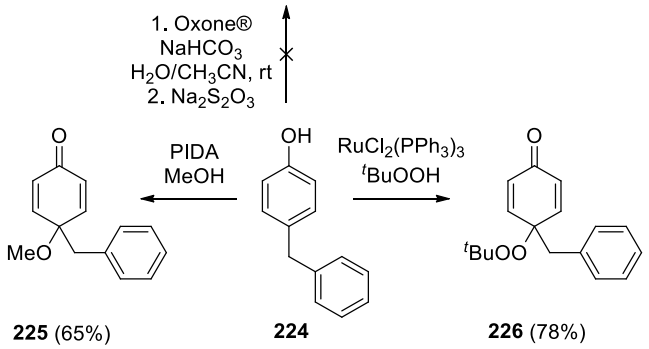
Figure 3.8

Unfortunately, this phenol behaves in a very different way in comparison with its analogous with one more methylene, affording in any case (using PIDA or Oxone®/$NaHCO_3$) a complex mixture of reaction (**Scheme 3.96**).



Scheme 3.96

Indolylethyl and indolylmethyl phenols **211** and **220** only differ in the nature of the methylene at the *para* position of the phenol, being more acidic (around 10 units of pKa) in the case of indolylmethyl phenol **220** than for phenol **211**. However, it is interesting to notice that comparing 4-(2-indolylmethyl)phenol **220** with its analogous 4-benzylphenol **224**, both with similar pKa of that methylene, they behave completely different in oxidative dearomatization reactions (**Scheme 3.97**). When 4-benzylphenol **224** reacts with PIDA using MeOH as solvent, a 65% isolated yield of the corresponding *O*-methyl substituted *p*-quinol **225** was obtained.[32b] In the ruthenium-catalyzed oxidation of 4-benzylphenol **224** with ^{t}BuOOH, a 78% of the corresponding hydroperoxy-*p*-quinol **226** was obtained[30h] (**Scheme 3.97**). In this last case, the proposed mechanism evolves through the phenoxenium cation intermediate (**intermediate B**, **Scheme 3.93**) as well as the dissociative mechanism in the PIDA oxidative dearomatization (**Scheme 3.93**). The negative results obtained in the oxidation of 4-(2-indolylmethyl)phenol **220** with PIDA are not in accordance with those obtained with its aromatic analogous 4-benzylphenol **224**. However, the complex mixture obtained when phenol **220** reacts with the mixture Oxone®/$NaHCO_3$ agrees with the result obtained in the case of 4-benzylphenol **224** (**Scheme 3.97**). As previously discussed in Chapter 2, the mechanism of the oxidative dearomatization of *p*-alkylphenols using Oxone®/$NaHCO_3$ starts with a Diels-Alder reaction between the aromatic phenol (behaves as a diene) and the singlet oxygen ($^1O_2$) (behaves as the dienophile). In the case of *p*-benzylphenols, the electronic density on the phenolic ring decreases as a consecuence of the conjugation with the benzyl ring. Thus, the phenolic ring is less reactive in terms of Diels-Alder reaction.

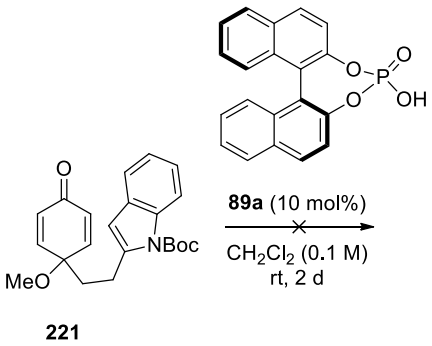


Scheme 3.97

Study of the intramolecular FC reaction of 4-(2-(1-*tert*-butylcarboxylate-indol-2-yl)ethyl)quinols 221 and 222.

With the *O*-methyl ether quinol **221** and free OH *p*-quinol **222** we developed the study of their behavior under FC experimental conditions.

Based on the good results obtained in the intermolecular FC reaction of quinols and indoles catalyzed by phosphoric acids, we initially treated the *N*-Boc *O*-methyl substituted *p*-quinol **221** with the phosphoric acid **89a** (10 mol%) in CH_2Cl_2. However, after 2 days, the starting material was recovered unaltered (**Scheme 3.98**).

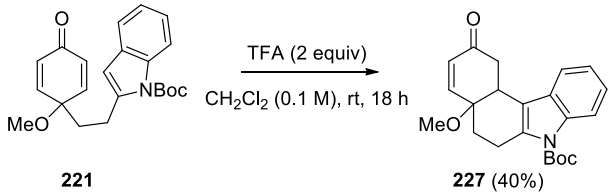


Scheme 3.98

In the intermolecular FC reaction of indoles to *p*-quinol we observed that the free OH of *p*-quinol was essential for the conjugate addition to the cyclohexadienone. A pausible

hydrogen bond, acting as a tether element to gain proximity to both nucleophile and electrophile partners was rationalized to be the origin of the reactivity.

In the present case, the indol is anchored directly through an ethyl group to the cyclohexadienone system, therefore, the lack of reactivity could be regarded to the *N*-Boc protecting group of the indol, that it is known to decrease the nucleophility of the indole core. A possible way to clarify this issue was to remove the Boc protecting group of **221**. To our surprise, treatment of the *N*-Boc indolyl ethyl *O*-methyl *p*-quinol **221** under the standard conditions for the *N*-Boc deprotection reaction[141] (excess TFA, CH_2Cl_2) kept the *N*-Boc protecting group unaltered and all the starting material was completely transformed into the FC alkylated product **227** in a 40% isolated yield (**Scheme 3.99**).

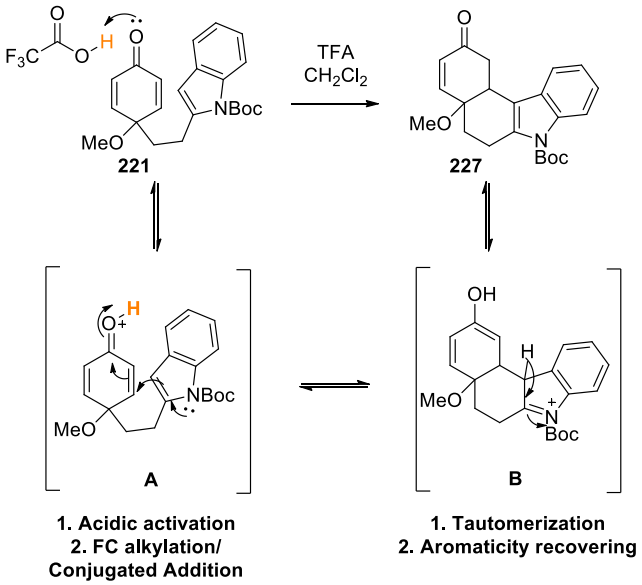


221 **227** (40%)

Scheme 3.99

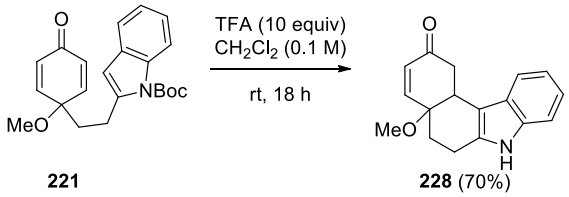
The proposed mechanism to obtain **227** as the only product is depicted in **Scheme 3.100**. TFA could act as a brønsted acid that protonated the oxygen of the carbonyl group, activating the cyclohexadienones towards the FC alkylation of the indole (**Intermediate A**). The resulting enol tautomerizes to the keton form and the indole core recovers the aromaticity by the elimination of a H^+ (**Intermediate B**) giving, at the end, compound **227**.

[141] Lundt, B. F.; Johansen, N. L.; Vølund, A.; Markussen, J. *Int. J. Peptide Protein Res.* **1978**, *12*, 258.



Scheme 3.100

The existence of several oxygen coordinating atoms could decrease the TFA effect in the deprotection process. Thus, we decided to perform the same reaction but using 10 equivalents of TFA. In this case, the *N*-H deprotected FC alkylated product **228** was obtained in 2 steps with an overall yield of 70% (**Scheme 3.101**).



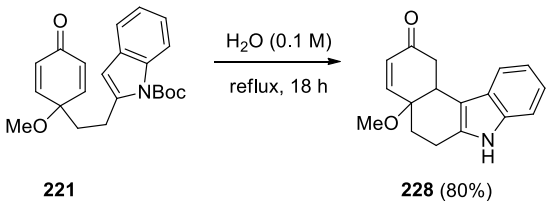
Scheme 3.101

Comparing the results obtained in **Scheme 3.99** and **Scheme 3.101** it could be assessed that the first step consists on the FC alkylation of *N*-Boc protected indole and the second step is the Boc removal in the presence of a high excess of TFA.

In the literature, Qu's group reported the boiling water-catalyzed neutral and selective *N*-Boc deprotection.[142] The possibility of removing the Boc group by using a green and cheap solvent such as water encouraged us to try it to our purpose: removing the Boc group under

[142] Wang, J.; Liang, Y.-L.; Qu, J. *Chem. Commun*. **2009**, 5144.

neutral conditions in order to see if it is possible to isolate the *N*-deprotected form of *p*-quinol **221**. Surprisingly, deprotected tetracycle derivative **228** was the only product obtained in two steps in a 80% overall isolated yield (**Scheme 3.102**). This evidences that once the Boc is removed, the electron rich indole reacts with the 2,5-cyclohexadienone moiety in the C-4 position independently the acidity of the media.



221 **228** (80%)

Scheme 3.102

The relative configuration of compounds **227** and **228** was assigned in base of the 2D ^{1}H-NMR spectra of **228**. Thus, the NOESY spectrum of compound **228** showed a cross peak between H-11c and the OMe group at C-4a, which confirm the *cis*-fusion of the 6-member ring formed in the conjugated addition (**Figure 3.9**).

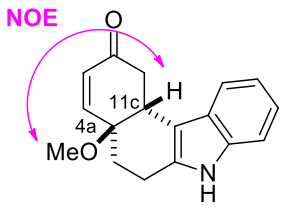
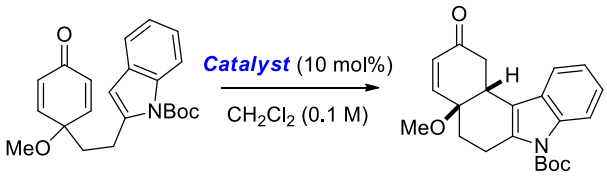


Figure 3.9

Based on the excellent results observed in the intermolecular iron (III)-catalyzed FC reaction of indoles and quinols previously reported in this doctoral work, we next studied the behavior of **221** towards the FC Lewis acid catalyzed reaction. Thus, when **221** was treated with $FeCl_3 \cdot 6H_2O$ (10 mol%) using CH_2Cl_2 as solvent at room temperature, only starting material was observed in the reaction crude after 2 days. A 10% conversion was obtained when the reaction was heated at reflux after 5 days (**Table 3.12, entries 1 and 2**). Similar results were obtained using $Cu(OTf)_2$ (10 mol%) as the Lewis acid in CH_2Cl_2. Thus, no conversion was observed at room temperature and a 30% of conversion was measured after heating at 50°C for 5 days (**Table 3.12, entries 3 and 4**).



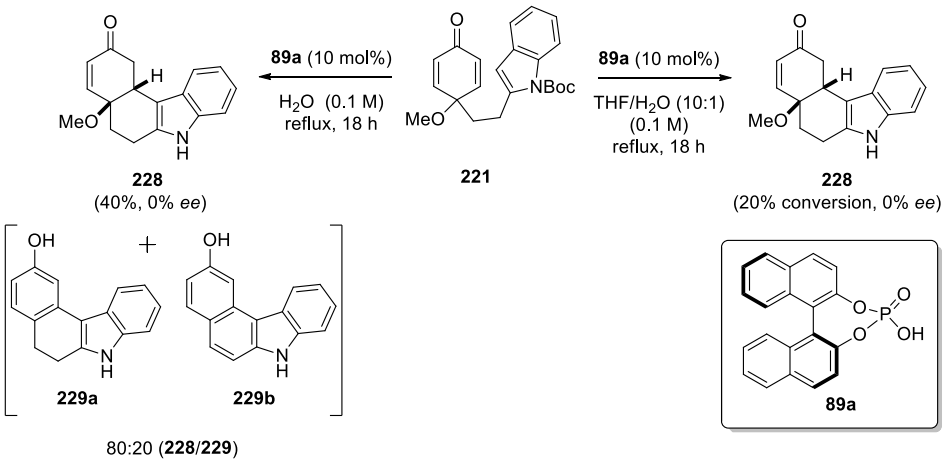
221 **227**

Entry	*Catalyst*	Time	T	Conversion to **227** (%)[a]
1	$FeCl_3 \cdot H_2O$	2d	rt	0
2		5d	50°C	10
3	$Cu(OTf)_2$	2 d	rt	0
4		5 d	50°C	30

[a] Conversion measured by ^{1}H-NMR spectroscopy of the crude

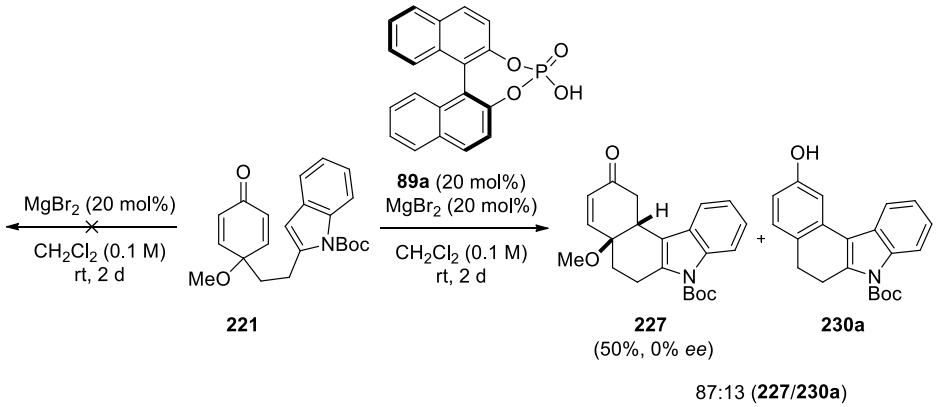
Table 3.12

In order to achieve better conversion and based on the good results obtained in the intermolecular FC process by using phosphoric acids derived from BINOL as catalysts, we decided to combine the phosphoric acid **89a** with a mixture of solvents, including H_2O in order to remove the *N*-Boc protecting group in the presence of a catalytic amount of a chiral acid (**Scheme 3.103**). Thus, we performed two different reactions changing the solvents: the combination of water with a miscible solvent and the use of water as the only solvent of the reaction. Treatment of **221** with a catalytic amount of **89a** in a 10:1 mixture of THF/H_2O at reflux, gave after 18 hours, compound **228** with a 20% of conversion as a racemic mixture (**Scheme 3.103**). Using H_2O exclusively as solvent, the reaction of *p*-quinol **221** with **89a** (10 mol%) gave, after 18 hours under reflux, a 80:20 mixture of the FC alkylated and arylated compounds **228** and **229**. Compound **228** was isolated in a 40% yield as a racemic mixture. Analysis of the ^{1}H-NMR revealed the existence of two FC arylated compounds, characterized as the 5,6-dihydrobenzo[*c*]carbazole compound **229a** and the aromatic analogue benzo[*c*]carbazole **229b**.



Scheme 3.103

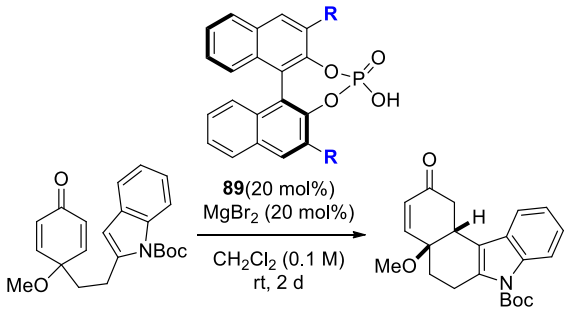
We also tested the combination of a Lewis acid and a Brønsted acid as a *binary catalyst*.[129] We chose a Mg^{2+} salt because it gave the best results concerning to enantioselectivity in the intermolecular version of FC. To our surprise, the reaction of *p*-quinol **221** with $MgBr_2$ (20 mol%) combined with the phosphoric acid **89a** (20 mol%) in CH_2Cl_2 (0.1 M) as solvent gave, after 2 days, a 87:13 mixture of **227**/**230a** from where the FC alkylated *N*-Boc protected derivative **227** was isolated in 50% yield, but in 0% *ee* (**Scheme 3.104**). When only $MgBr_2$ was used as catalyst in the same experimental conditions described above, the starting material was recovered unaltered (**Scheme 3.104**).



Scheme 3.104

Encouraged for the good reactivity observed with a combination of a Lewis acid and a phosphoric acid at room temperature, we screened different phosphoric acids in order to observe an enantioselective induction in the synthesis of **227**.

Four phosphoric acids **89a-c** and **89g** were tested. In the case of phosphoric acid unsubstituted BINOL derivative **89a** (**Table 3.13, entry 1**) and sterically hindered **89b** and **89c** (**Table 3.13, entries 2 and 3**) the conversion and yields were good, but the enantiomeric excess was null. On the contrary, in the case of phosphoric acid **89g**, no reaction was observed (**Table 3.13, entry 4**).



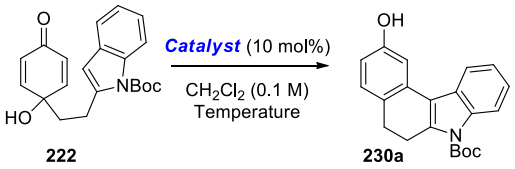
221 **227**

Entry	**89** (R)	Time	Yield(%)[a]	*ee* (%)[b]
1	**89a** (H)	2 d	50	0
2	**89b** (2,4,6-(^{i}Pr)$_3$C$_6$H$_2$)	2 d	50	0
3	**89c** (3,5-(CF$_3$)$_2$C$_6$H$_3$)	2 d	61	0
4	**89g** (9-Antracyl)	2 d	No reaction	-

[a] Isolated yield; [b] enantiomeric excess measured by HPLC analysis

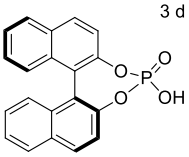
Table 3.13

We next study the FC reactivity of the free OH indolylethyl *p*-quinol **222**. The reactivity of *p*-quinol **222** towards Lewis and brønsted acids is shown in **Scheme 3.105**. When a CH_2Cl_2 solution of **222** was treated with $FeCl_3{\cdot}6H_2O$ (10 mol%) at room temperature, after 2 days only starting material was detected by GC-MS. Heating he reaction at 50°C the 5,6-dihydrobenzo arylated FC product **230a** was obtained in a 50% conversion. Using $Cu(OTf)_2$ as Lewis acid, phosphoric acid **89a** or *p*TSA as brønsted acids, similar results were obtained. In contrast to the *O*-methyl-(indolylehtyl)-*p*-quinol derivative **221**, the free OH indolylethylquinol **222** gave the FC arylated compound dihydrobenzo[*c*]carbazole **230a** and the FC alkylated derivative was not observed.



Catalyst:	Lewis Acid	time	T	Conversion (%)[a]
	$FeCl_3 \cdot 6H_2O$	2 d	rt	0
		3 d	50°C	<50
	$Cu(OTf)_2$	2 d	rt	0
		3 d	50°C	<50

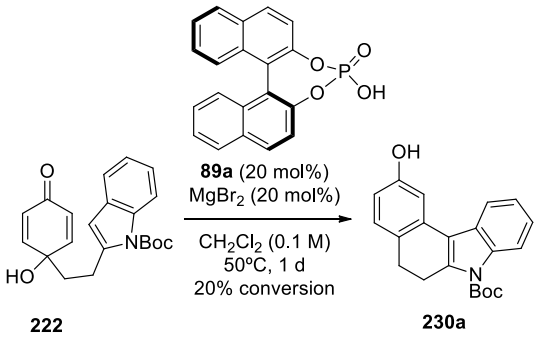
Brønsted Acid	time	T	Conversion (%)[a]
*p*TSA	2 d	rt	0
	3 d	50°C	<50
93a	2 d	rt	0
	3 d	50°C	<50



[a] Conversion measured by ^{1}H-NMR spectroscopy of the crude

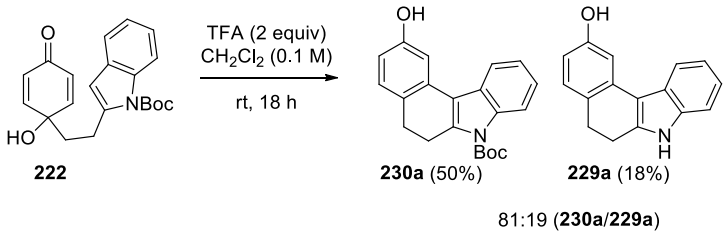
Scheme 3.105

The intramolecular FC reaction of *p*-quinol **222** using the combination of phosphoric acid **89a** and $MgBr_2$ as binary catalyst only occurred when heating the reaction at 50°C to give the dihydrobenzo[*c*]carbazole **230a** although in 20% of conversion (**Scheme 3.106**). In this case, the desired FC alkylated product was not observed.



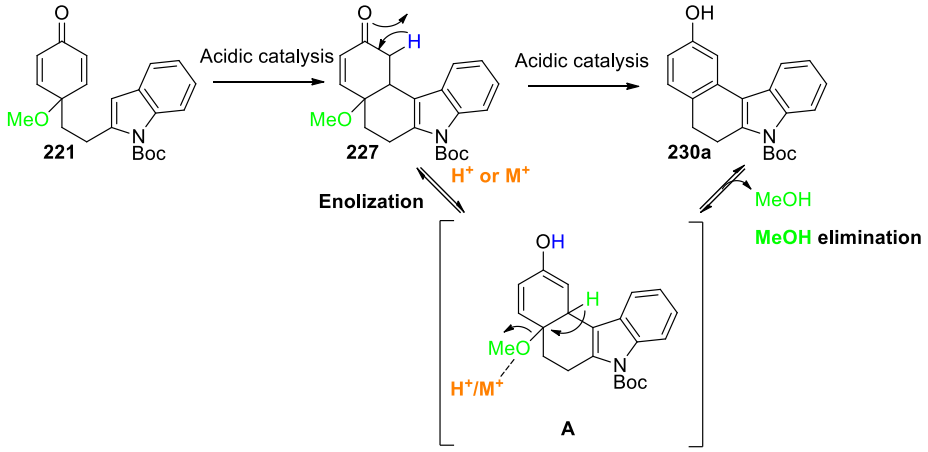
Scheme 3.106

The reaction of *p*-quinol **222** with TFA (2 equiv) as brønsted acid, gave after 18 hours a 81:19 mixture of **230a**/**229a** which could be isolated pure in a 50% and 18% yield respectively (**Scheme 3.107**).



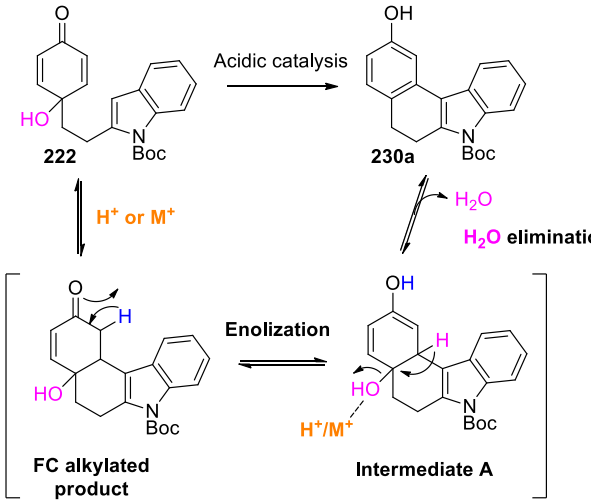
Scheme 3.107

Formation of compound **230a** in an acidic media (Lewis acid catalysis or Brønsted acid catalysis) from *N*-Boc-*O*-methyl-*p*-quinol **221** could be explained from isolated FC alkylated product **227**. Thus, in the presence of acidic conditions, the enol tautomer could be favored (**Intermediate A**) and the possibility of aromatizing a 6-member ring could be the driving force by means of the elimination of MeOH affording **230a** (**Scheme 3.108**).



Scheme 3.108

Formation of compound **230a** from *p*-quinol **222** in acidic conditions, could be explain in a similar manner but, in this case, the isolation of the FC alkylated product is not observed. As it is shown in **Scheme 3.109**, after the FC alkylation reaction, an enolization process takes place affording **intermediate A** which, after the loss of a molecule of H_2O aromatizes giving dihydrobenzo[*c*]carbazole **230a** as the only observed product.



Scheme 3.109

Study of the intramolecular FC reaction of 4-(2-(1-*tert*-butylcarboxylate-indol-2-yl)ethyl)phenol 211.

So far, tetrahydro and dihydrobenzo[*c*]carbazoles have been synthetized from *p*-quinol derivatives **221** and **222** (**Figure 3.10**). We wondered if the same products could be obtained directly from phenol **211** without the isolation of quinols derivatives by means of domino sequences (**Figure 3.10**).

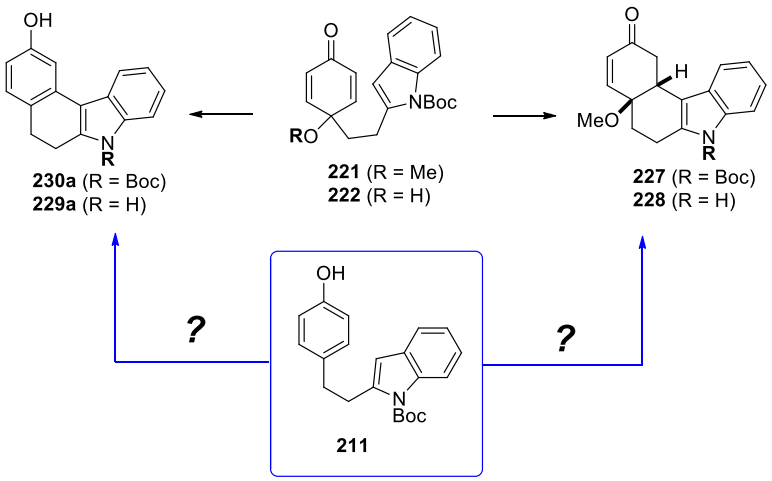
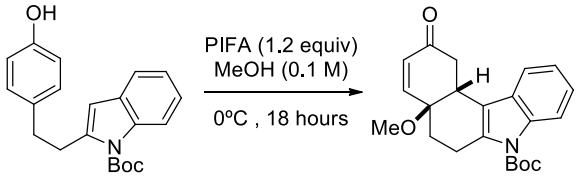


Figure 3.10

Thus, we further studied the reactivity of phenol **211** with PIFA (Phenyllodine bis(trifluoroacetate)) because this hypervalent iodine reagent generates TFA in the reaction media and this could be used to gain, by a domino sequence, a direct access to the FC products.

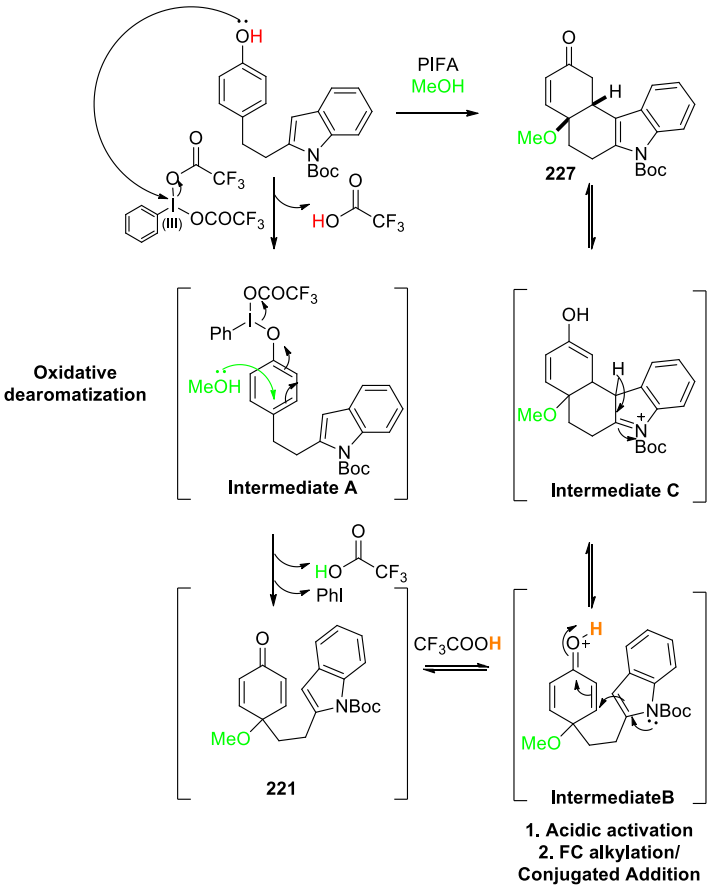
When phenol **211** was treated with PIFA (1.2 equiv) in a methanolic solution at 0°C (**Scheme 3.110**), the FC alkylated product **227** was isolated in a 44% overall yield in a domino sequence of two steps that involves an oxidative dearomatization followed by a conjugate addition of the indole to the cyclohexadienone framework.



211 **227** (44%)

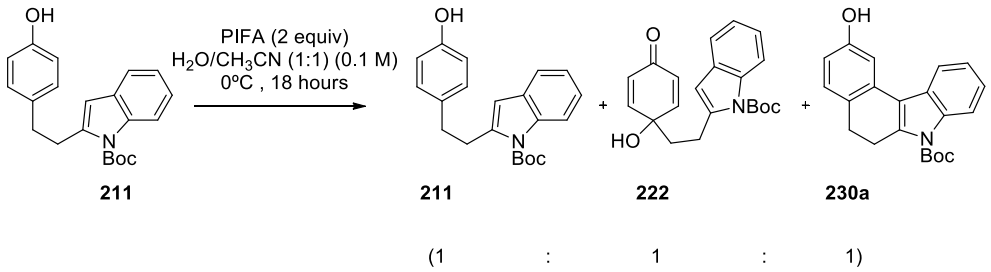
Scheme 3.110

The difference in acidity of the acetic acid (pk_a = 4.76 (measured in H_2O)) and trifluoroacetic acid (pk_a = -0.25) which are generated during the reaction of **211** with PIDA or PIFA respectively, could be the origin of the different reactivity observed in both cases. The proposed mechanism for the formation of compound **227** is depicted in **Scheme 3.111**. The first step begins by the oxidative dearomatization of phenol **211** with the hypervalent iodine PIFA to form **Intermediate A** and TFA. Then the nucleophile (MeOH), attacks to the *para*-carbon generating PhI and TFA affording *O*-methyl protected quinol **221** which is not isolated. In the second step, the TFA protonates the carbonyl group favoring the FC alkylation reaction of indol on the α,β-usaturated position of the cyclohexadienone moeity (**Intermediate B**). The resulting enol tautomerizes to the keto form and the indole core recovers the aromaticity by the elimination of a proton (**Intermediate C**) giving compound **263**.



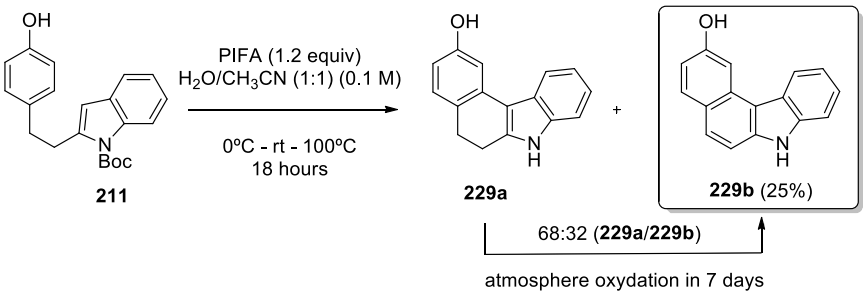
Scheme 3.111

To gather more information about the reactivity of **211**, we ran the reaction of **211** with PIFA as oxidant using a 1:1 mixture of H_2O/CH_3CN. After a few hours of reaction, a mixture of starting material **211**, *p*-quinol **222** and FC arylated compound **230a** was observed in the crude in a 1:1:1 ratio (**Scheme 3.112**). More equivalents of PIFA did not afford better results.



Scheme 3.112

When the reaction temperature was rised from 0°C to room temperature, and then to 100°C when all the starting material was not observed in the crude, after 18 hours, a 68:32 mixture of FC arylated **229a**/**229b** was observed (**Scheme 3.113**). Interestingly, after 7 days, the mixture evolved to the totally oxidized benzo[*c*]carbazole **229b** with a 25% overall yield. Compound **265b** was obtained in a one-pot sequence of five steps that embrace an *oxidative dearomatization, N-Boc deprotection, conjugated addition, water elimination and dehydrogenation*.



Scheme 3.113

Since oxidation of the *N*-Boc derivative **230a** to the aromatic compound **230b** was never observed we could stablished that only electron rich N-H-free compound **229a** is able to dehydrogenate to afford **229b** (**Figure 3.11**).

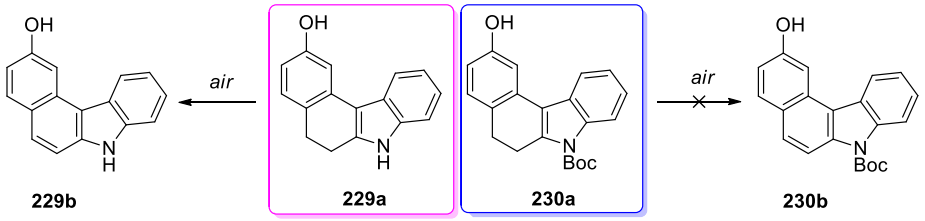
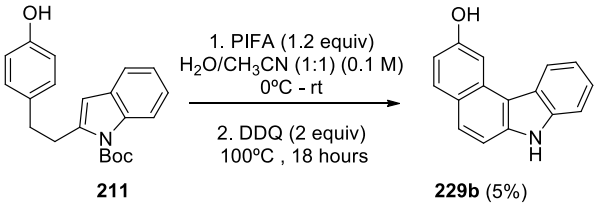


Figure 3.11

Attempts to oxidize compound **229a** to **229b** using DDQ (2 equiv) at 100°C for 18 hours, gave product **229b**, although contaminated with an unknown subproduct in a 75:25 mixture (**229b**/unknown product). Unfortunately, purification by preparative TLC afforded only a 5% yield of **229b** (**Scheme 3.114**).

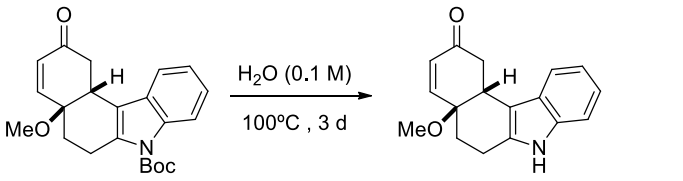


211 **229b** (5%)

Scheme 3.114

Derivatization of FC alkylated and arylated products.

Deprotection of N-Boc derivative **227** under the water boiling gave, after 3 days, the desired NH free product **228**, in moderate conversion (41%) (**Scheme 3.115**).

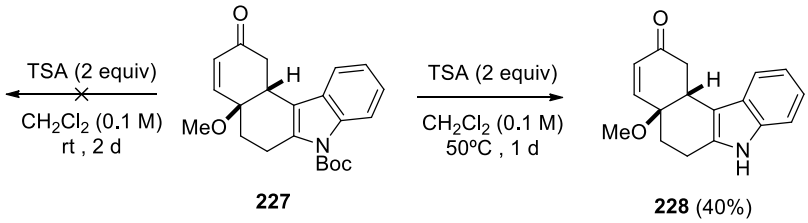


227 **228** (41% conversion)

Scheme 3.115

In order to check the possibility of transform FC alkylated product **227** into the more oxidized 5,6-dihydrobenzo[*c*]carbazole FC arylated compound **230a**, it was treated with *p*TSA (1 equiv) in CH_2Cl_2 at room temperature. Unfortunately, after 2 days, the starting material kept unaltered (**Scheme 3.116**). However, when running the reaction under reflux, *N*-Boc protected

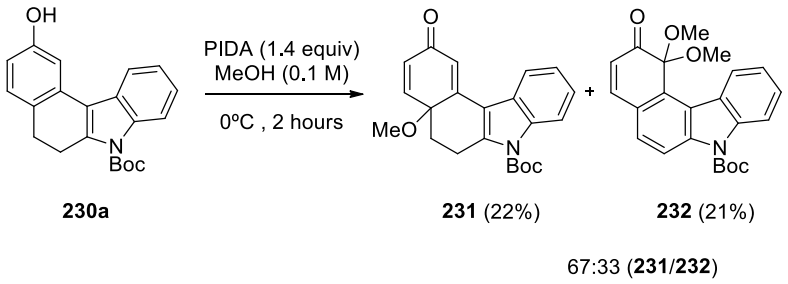
FC alkylated product **227** transforms into its deprotected form **228** in a 40% isolated yield in 1 day (**Scheme 3.116**). In both cases, the arylated FC product **230a** was not observed.



227 **228** (40%)

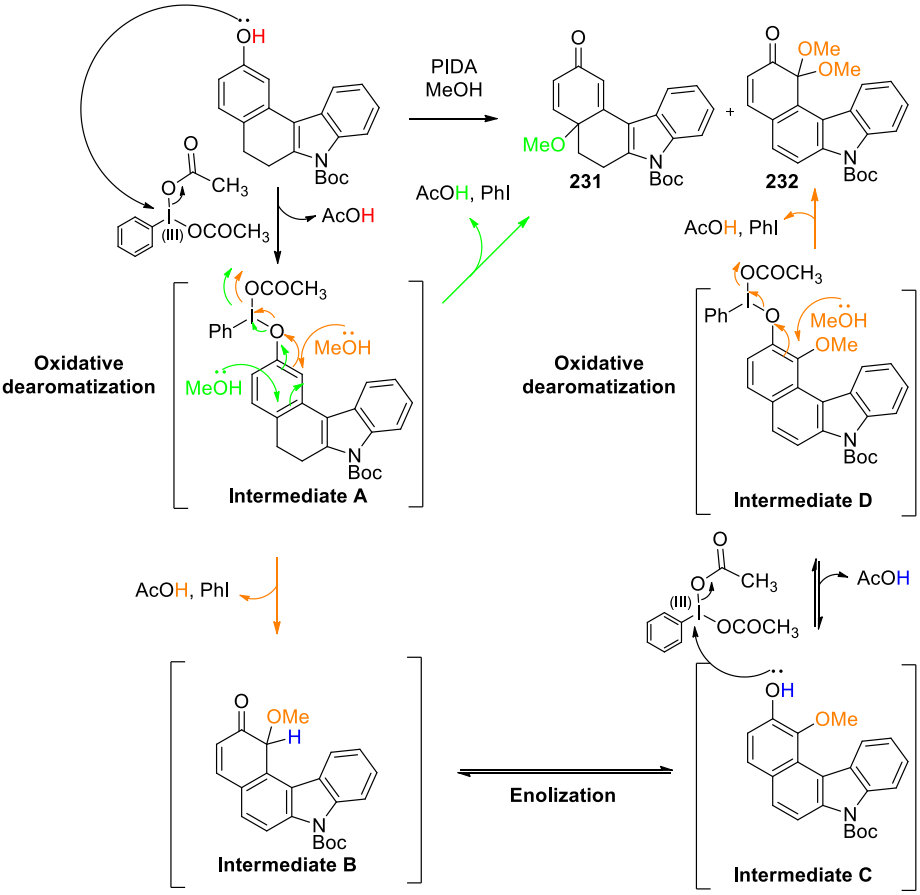
Scheme 3.116

Encouraged by the results obtained in the one-pot preparation of benzo[*c*]carbazoles starting from *p*-phenols, we decided to explore the behavior of the *p*-alkyl phenol **230a** synthetized before with this methodology. Thus, reaction of phenol **266a** with 1.4 equivalents of PIDA in a methanolic solution at 0°C, gave a 67:33 mixture of racemic *O*-methyl protected *p*-quinol **231** and the *ortho* monoketal **232** in 22 and 21% isolated yield respectively (**Scheme 3.117**).



Scheme 3.117

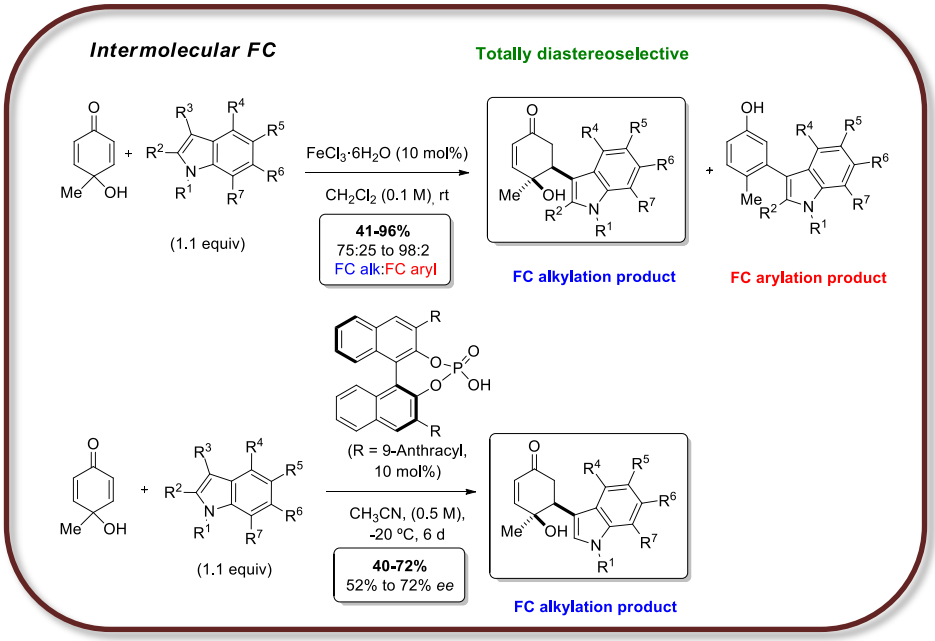
The proposed mechanism for the synthesis of both derivatives **231** and **232** is shown in **Scheme 3.118**. The first step is the oxidative dearomatization of the starting phenol **230a**. As it has been previously reported in this chapter, the "phenolic umpolung" (**Intermediate A**) leads to the attack of nucleophile (in this case MeOH) in two possible positions: *ortho* and *para*. When the attack occurs in the *para*-carbon, the resulted product is *O*-methyl protected **231**. However, the *ortho*-carbon attack gives **Intermediate B** which, after enolization to afford **Intermediate C** could suffer other "phenolic umpolung" with a second molecule of PIDA (**Intermediate D**) allowing the second *ortho* attack of a MeOH molecule, obtaining at the end the *ortho*-monoketal **232** (**Scheme 3.118**).


PIDA
MeOH
231
232
AcOH, PhI
AcOH
Oxidative dearomatization
Intermediate A
Oxidative dearomatization
Intermediate D
AcOH, PhI
Enolization
Intermediate B
Intermediate C

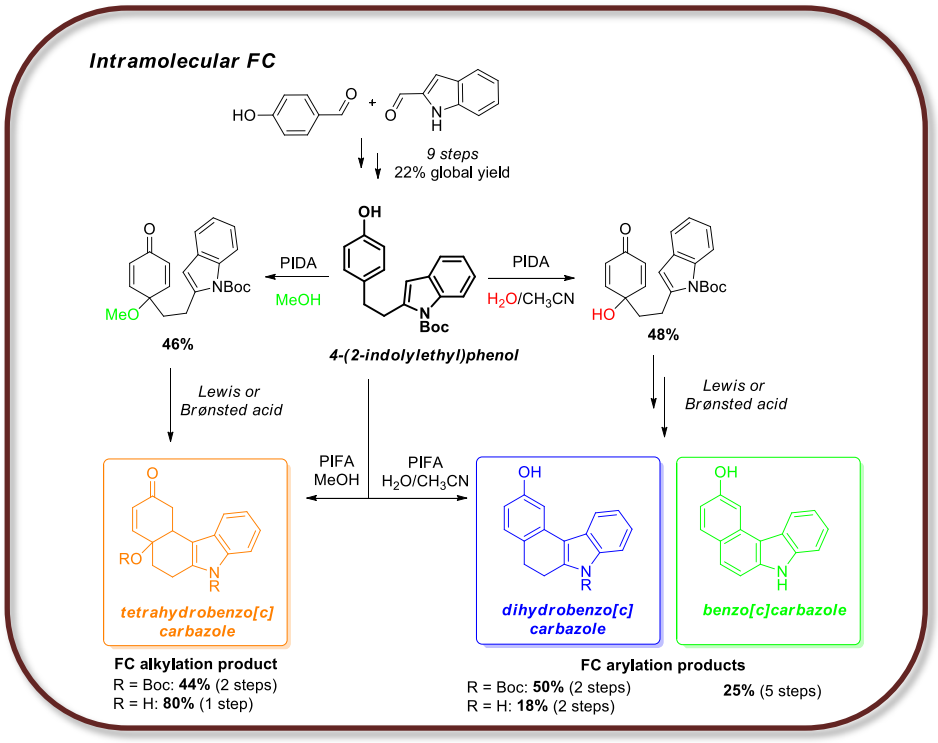
Scheme 3.118

Study of Friedel-Crafts reactions of *p*-quinols with different heteroaromatic derivatives:

As a summary of Chapter 3, in **Scheme 3.119** are shown the most important results obtained in the intermolecular FC reactions of heteroaromatic derivatives with *p*-quinols and in **Scheme 3.120** the best results in the intramolecular FC reactions of 4-(2-indolylethyl)quinols.



Scheme 3.119



Scheme 3.120

Chapter 4

Conclusions

4. Conclusions.

The development of this Ph D thesis allows establishing the following conclusions:

1. **Study of base catalyzed reactions of p-quinols with aldehydes and imines.**

1.1. Base catalyzed reactions of p-quinols with aldehydes.

The reaction of *p*-quinols with aromatic and heteroaromatic aldehydes in the presence of 15 mol% de DMAP as base and CH_2Cl_2 as solvent afforded, in a stereoselective manner, the *cis*-dihydrobenzo-[1,3]-dioxol-5(7a*H*)-ones **73**, **84** and **86** respectively with good to excellent yields. When TMSOTf is used as Lewis acid in the reaction of 4-hydroxy-4-methyl-2,5-cyclohexadienone with 2-pyridine carbaldehyde, diastereoselectivity of compound **86a** was inverted to respect the diastereoselectivity obtained using DMAP/CH_2Cl_2 when an excess of TMSOTf was used. The reaction of *p*-quinols with aliphatic aldehydes afforded the *cis*-dihydrobenzo-[1,3]-dioxol-5(7a*H*)-one derivatives **88** with good diastereoselectivity and yield, only when a phosphoric acid derived from BINOL was used as the catalyst in CH_2Cl_2 as solvent (**Scheme 4.1**).

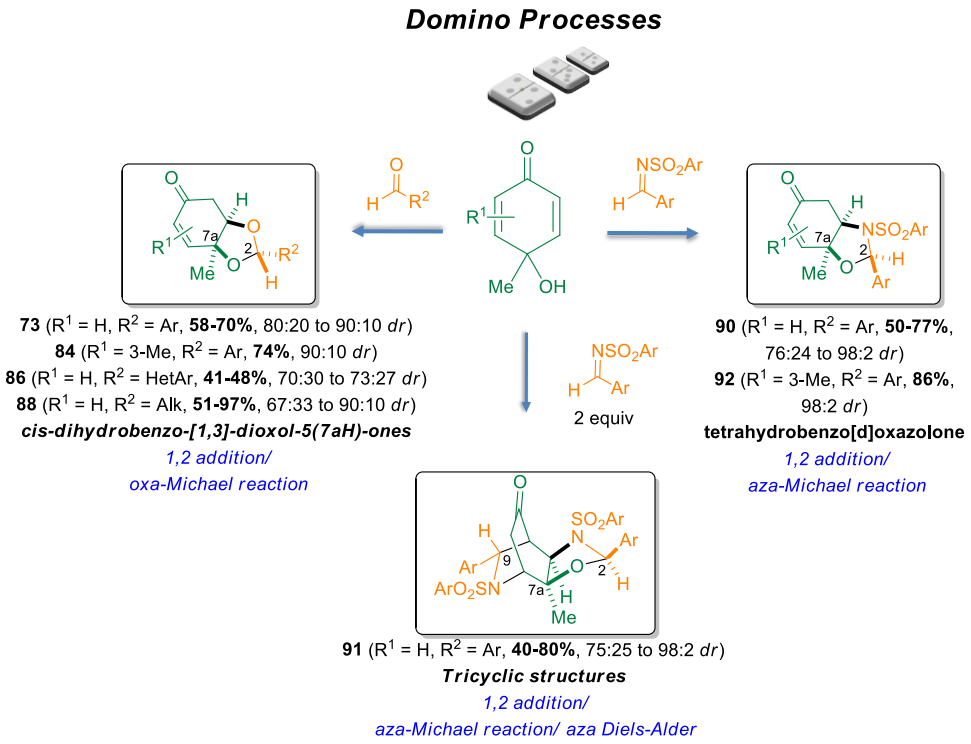
The formation of these *cis*-dihydrobenzo-[1,3]-dioxol-5(7a*H*)-one derivatives is the result of a 1,2-addition of the hydroxy group at C-4 of *p*-quinol to the carbonyl group of the corresponding aldehyde followed by an intramolecular oxa-Michael addition to one of the double bonds of the cyclohexadienone moiety. The stereochemical course of all reactions has been proposed.

1.2. Base catalyzed reactions of p-quinols with sulfonyl aryl imines.

The reaction of *p*-quinols with sulfonyl aryl imines differently substituted in the sulfonyl and the aryl moiety catalyzed by a base afforded polyheterobicyclic **90** and **92** or tricyclic **91** structures, depending on the base. Thus, when the catalytic system was DMAP (15 mol%) in CH_2Cl_2 as solvent the tetrahydrobenzo[*d*]oxazolone derivatives **90** and **92** were obtained. Using DABCO (15 mol%) as catalyst with 70 mol% of $LiClO_4$ as an additive in THF as solvent, allowed the diastereoselective access to polyheterotricyclic structures **91** which contained a piperidine and a oxazolidine fragment in their skeleton (**Scheme 4.1**).

Structures **90** and **92** were the result of a 1,2-addition of the nucleophilic OH group at C-4 of *p*-quinol to the electrophilic imine followed by the intramolecular aza-Michael addition to one of the two double bonds of the cyclohexadienone moeity. The formation of tricyclic structures

91, resulting when the catalytic system DABCO/ $LiClO_4$ in THF was used, could be explained by a 1,2-addition reaction followed by the intramolecular aza-Michael addition as well as mentioned above. The resulting enolate after the aza-Michael addition behaves as a diene in an aza Diels-Alder reaction with another molecule of imine affording the tricyclic structures with excellent diastereoselectivity and moderate yields. The stereochemical course of all reactions has been proposed.



Scheme 4.1

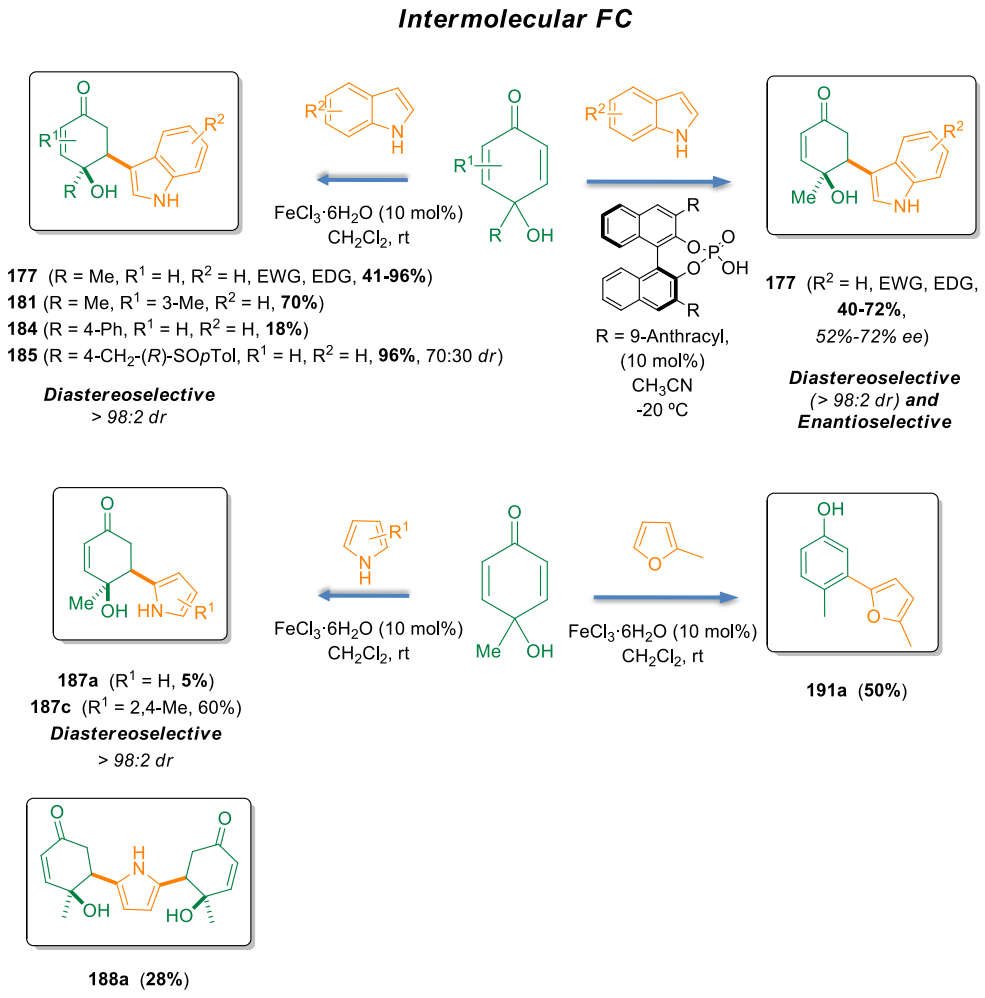
2. Study of the Friedel-Crafts reaction of *p*-quinols with different heteroaromatic derivatives.

2.1. Intermolecular Friedel-Crafts reactions of p-quinols with heteroaromatic derivatives.

In the Fe(III)-catalyzed alkylation of indoles using *p*-quinols as electrophiles, a conjugate addition of the indole to the cyclohexadienone moiety was always observed (**177**). The approach of the nucleophile occurs by the face containing the hydroxy group, in a highly diastereoselective manner. The better catalytic system for such FC alkylation was $FeCl_3 \cdot 6H_2O$ (10 mol%) in CH_2Cl_2 as solvent. The use of differently substituted indoles and *p*-quinols afforded good yields of **177**, **181**, **184** and **185** derivatives whereas the use of pyrrols did not allow generalizing the reaction, obtaining low yields of the conjugated addition product (**187a,**

187c). Only in the case of unsubstituted pyrrol a double FC alkylation occurred in 28% yield (**188a**).The use of furans afforded exclusively the arylated FC product **191a** whereas in the case of tiophens the alkylation product was not observed in any case (**Scheme 4.2**).

The use of an enantiopure phosphoric acid derived from BINOL bearing two anthracyl fragments at the biraryl fragment as catalyst, allowed the reaction of 4-hydroxy-4-methyl-quinol with differently substituted indoles affording the FC alkylated products **177** in moderate to good yields (40 to 72%), excellent diastereoselectivities and moderate enantioselectivities (from 52%-72% *ee*) (**Scheme 4.2**).

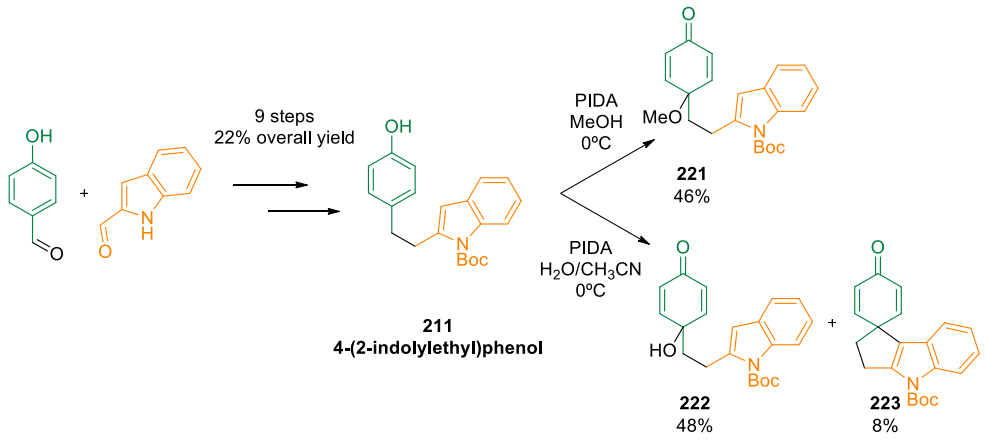


Scheme 4.2

2.2. Intramolecular Friedel-Crafts reaction of para- and ortho-(2-indolylalkyl)quinols.

The 4-(2-indolylethyl)phenol **211** derivative was synthetized for the first time in 9 steps with a overall yield of 22% from commercially available starting materials (**Scheme 4.3**).

In the oxidation of 4-(2-indolylethyl)phenol **211** with PIDA in MeOH, the 4-methoxy derivative **221** was obtained in 46% yield and the 4-hydroxy derivative **222** resulted in 48% yield when H_2O was present in the reaction medium. In this case, a 8% yield of the spirocycle **223** resulting in the intramolecular addition of the indole fragment during the oxidation process was isolated (**Scheme 4.3**).

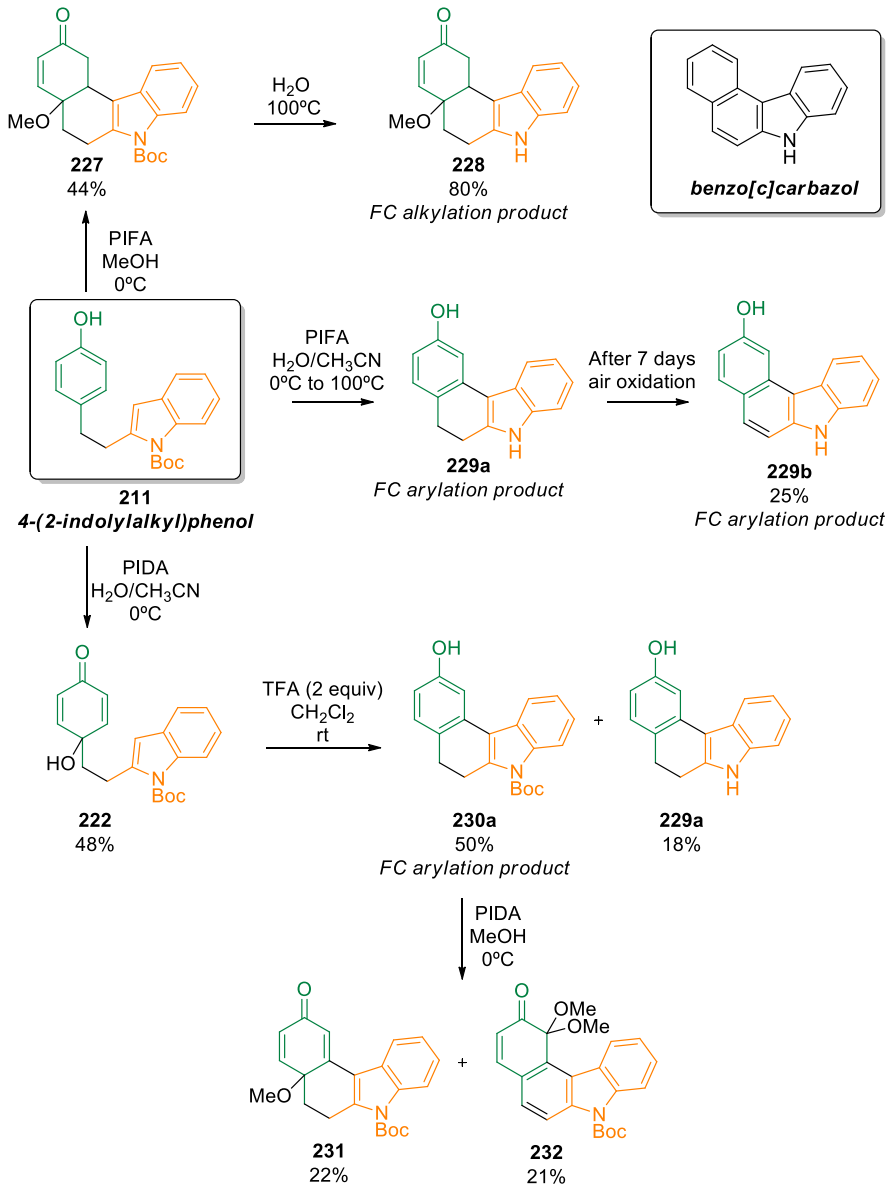


Scheme 4.3

A study of the reactivity of phenol **211** was developed in order to obtain selectively by means of domino processes different structures with hydrobenzo or benzo[*c*]carbazol skeleton. The best results were summarized in **Scheme 4.4**. When compound **211** is treated with PIFA in MeOH, the methoxy substituted tetracycle **227** (FC alkylated product) was obtained in 44% yield. This compound **227** was refluxed in H_2O as solvent affording *N*-deprotected derivative **228** in 80% yield.

The treatment of 4-(2-indolylethyl)phenol **211** with PIFA but using H_2O/CH_3CN as solvent at 0°C and then heated at 100°C afforded deprotected 5,6-dihydrobenzocarbazole (FC arylated product) **229a** which, after 7 days under air oxidation transformed into benzo[*c*]carbazole **229b** in 25% yield after 5 steps (phenolic oxidation, *N*-Boc deprotection, FC alkylation, enolization-H_2O elimination, double bond oxidation). As mentioned above, the reaction of 4-(2-indolylethyl)phenol **211** with PIDA in H_2O/CH_3CN afforded as the major product *p*-quinol **222** in 48% yield. After treatment of **222** with TFA in CH_2Cl_2 a mixture of the FC arylated

products 5,6-dihydrobenzo[*c*]carbazole *N*-Boc protected **230a** and the deprotected **229a** (50% and 18% isolated yield respetively) was isolated. In order to obtain different structures, hydrocarbazole **230a** was treated with PIDA in MeOH and a mixture of the 2-oxo-5,6-dihydrobenzo[*c*]carbazole **231** and the ortho monoketal derivative **232** were obtained in 22% and 21% yield.



Scheme 4.4

Chapter 5

Experimental Part

5. Experimental Part.

5.1. General considerations.

Commercially available reagents were used without additional purification. Reagents were weighted on air. Subsequent work-up was performed on air. All reactions were monitored by thin-layer chromatography that was performed on precoated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230-400 mesh) of Merck. Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was flame-dried under a stream of dry argon.

For the preparation of starting materials which require anhydrous conditions, THF (SDS, anhydrous, analytical grade), CH_2Cl_2 (SDS, anhydrous, analytical grade), and toluene (SDS, anhydrous, analytical grade) were further dried by standing with activated 4Å molecular sieves for 7 days prior to use.

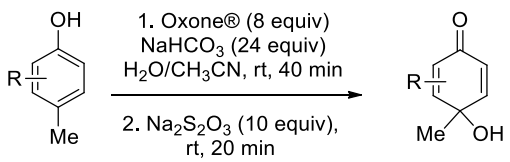
NMR spectra were recorded at 23 °C on the following spectrometer: Bruker AC-300 (300 MHz in ^{1}H, and 75 MHz in ^{13}C, 96 Hz in ^{11}B) in $CDCl_3$ with the solvent signal serving as internal standard at 7.26 ppm in ^{1}H-NMR and 77.0 ppm in ^{13}C-NMR or and acetone-d_6 with the solvent signal serving as internal standard at δ 2.1 ppm. The coupling constants (*J*) are reported in Hz and the chemical shifts (δ) in ppm. Mass spectra (FAB, EI and Electrospray (ESI)) were reported on a GCT Walters spectrometer coupled to a chromatogram of gases (model 6890N of a Agilent technologies). Melting points were determined using a Buchi apparatus.

5.2. Experimental procedures

EXPERIMENTAL PART OF CHAPTER 2: Study of base catalysed reactions of *p*-quinols with aldehydes and imines.

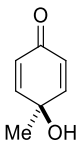
General procedure for the synthesis of *p*-quinols using Oxone®

GENERAL PROCEDURE A.[36]



A mixture of the corresponding *p*-alkyl phenol (1 equiv), water and CH_3CN (variable volume, see each individual case) (0.04 M) was vigorously stirred until complete solution of all starting material. A mixture of Oxone (8 equiv) and $NaHCO_3$ (24 equiv), previously ground into powder, was slowly added portion wise but without stop. A septum with an empty balloon was immediately placed to avoid overpressure into the flask and loss of generated singlet oxygen. The mixture was vigorously stirred until total disappearance of the phenol (monitored by TLC). After the time required, the crude reaction mixture was diluted with water. Solid $Na_2S_2O_3$ (10 equiv) was added in portions without stop for 3 minutes and the mixture was stirred at 25-28 °C for 30 min. The reaction was quenched with water and extracted with EtOAc. Combined organic extracts were dried (Na_2SO_4) and the solvent was eliminated in vacuo to yield pure *p*-quinols without need of further purification unless otherwise stated.

4-Hydroxy-4-methyl-2,5-cyclohexadien-1-one 3.



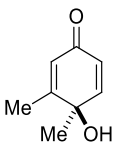
3

Following the general procedure **A**, *p*-cresol **1** (1.1 g, 10 mmol) was dissolved in a 4:1 mixture of H_2O (167 ml)/CH_3CN (42 ml). Then, Oxone® (50 g, 80 mmol) and $NaHCO_3$ (20 g, 240 mmol) were added and the reaction was stirred at room temperature until the consumption of the starting material. Then, the crude reaction was diluted with 100 ml of H_2O and $Na_2S_2O_3$ (16 g, 100 mmol) were added. After 30 min, the reaction was quenched with water and extracted with AcOEt affording 1 g (81% yield) of **3** which was used without further purification.

Synthesis from the p-benzoquinone dimethyl monoketal:[28a] To a solution of the *p*-benzoquinone monoketal **44** (4.85 g, 31.5 mmol) in dry THF (40 ml, 0.8 M) was added dropwise over a period of 10 min, a solution of MeLi (19.6 ml, 1.6 M in ether, 1 equiv) in THF (40 ml, 0.8 M) at -78 °C. After the addition was complete the mixture was stirred at room temperature for 3 hours and quenched with NH_4Cl and extracted with EtOAc. Combined organic layers were dried over Na_2SO_4 and the solvent was eliminated in vacuo. The resulting ketal derivative **74** was dissolved in a 10:1 mixture of THF/H_2O and 5 mol% of oxalic acid (1.55 mmol, 196 mg) was added. After 1 hour at room temperature the reaction was neutralized with a saturated solution of $NaHCO_3$ and extracted with EtOAc. Combined organic layers were dried over Na_2SO_4 and the solvent was eliminated in vacuo. Purification by flash column chromatography (EtOAc/Hexane: 3:2) gave **3** as a white solid. Yield: 2.42g (62%).

^{1}H NMR (300 MHz, $CDCl_3$):[36] δ = 6.83 (d, *J* = 9.7 Hz, 2H), 6.00 (d, *J* = 9.7 Hz, 2H), 3.78 (br s, 1H), 1.40 (s, 3H).

4-Hydroxy-3,4-dimethyl-2,5-cyclohexadien-1-one 77.

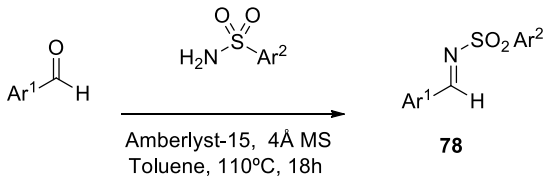

77

Following the general procedure **A**, *p*-alkylphenol **75** (1.22 g, 10 mmol) was dissolved in a 4.3:1 mixture of H_2O (167 ml)/CH_3CN (39 ml). Then, Oxone® (50 g, 80 mmol) and $NaHCO_3$ (20 g, 240 mmol) were added and the reaction was stirred at room temperature until the consumption of the starting material. Then, the crude reaction was diluted with 100 ml of H_2O and $Na_2S_2O_3$ (16 g, 100 mmol) were added. After 30 min, the reaction was quenched with water and extracted with AcOEt affording 993 mg (72% yield) of **77** which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$):[36] δ = 6.85 (d, *J* = 10.0 Hz, 1H), 6.10 (dd, *J* = 10.0 and 1.7 Hz, 1H), 6.00 (m, 1H), 3.39 (br s, 1H), 2.04 (d, *J* = 0.9 Hz, 3H), 1.40 (s, 3H).

General procedure for the synthesis of sulfonyl benzaldimines, sulfonyl α,β-unsaturated imines and ketimines

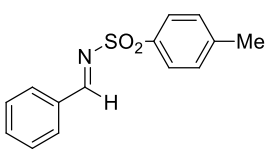
GENERAL PROCEDURE B.[56]



78

A mixture of the corresponding benzaldehyde (1 equiv), *N*-tosylamide (1 equiv), activated 4Å MS (1g/mmol) and a catalytic amount of Amberlyst 15 in dry toluene (1 M) was refluxed for 18 hours. When all the starting materials are consumed, the crude reaction is filtered over a pad of celite and evaporated under vacuum. The corresponding sulfonyl benzaldimine **78** is obtained pure by recrystallization from a 1:1 mixture of diethyl ether/hexanes.

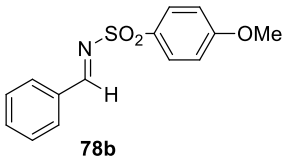
***(E)*-N-benzylidene-4-methylbenzenesulfonamide 78a.**


78a

Following the general procedure **B**, benzaldehyde (1.02 ml, 10 mmol), *p*-toluenesulfonylamide (1.71 g, 10 mmol), 4Å MS (10 g) and a catalytic amount of Amberlyst 15 in 10 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recristalization 2.3 g (92% yield) of **78a** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[143] δ = 9.00 (s, 1H), 7.90 – 7.85 (m, 4H), 7.60 – 7.58 (m, 1H), 7.47 – 7.44 (m, 2H), 7.32 – 7.30 (m, 2H), 2.39 (s, 3H).

***(E)*-N-benzylidene-4-methoxybenzenesulfonamide 78b.**

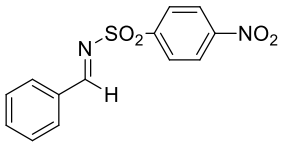


78b

Following the general procedure **B**, benzaldehyde (0.51 ml, 5 mmol), *p*-methoxysulfonylamide (936 mg, 5 mmol), 4Å MS (5 g) and a catalytic amount of Amberlyst 15 in 5 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recristalization 206 mg (15% yield) of **78b** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[144] δ = 8.98 (s, 1H), 7.91 – 7.87 (m, 4H), 7.60 – 7.55 (m, 1H), 7.47 – 7.42 (m, 2H), 7.00 – 6.96 (m, 2H), 3.83 (s, 3H).

***(E)*-N-benzylidene-4-nitrobenzenesulfonamide 78c.**

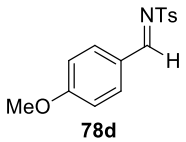


78c

Following the general procedure **B**, benzaldehyde (1.63 ml, 16 mmol), *p*-nitrosulfonylamide (3.24 g, 16 mmol), 4Å MS (16 g) and a catalytic amount of Amberlyst 15 in 16 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recrystallization 1.1 g (24% yield) of **78c** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[145] δ = 9.13 (s, 1H), 8.41 – 8.38 (d, *J* = 8.9 Hz, 2H), 8.23 – 8.20 (d, *J* = 8.9 Hz, 2H), 7.97 – 7.94 (m, 2H), 7.60 – 7.65 (t, *J* = 7.5 Hz, 1H), 7.56 – 7.50 (t, *J* = 7.6 Hz, 2H).

***N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide 78d.**



78d

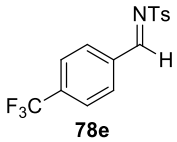
Following the general procedure **A**, 4-methoxybenzaldehyde (0.86 ml, 7 mmol), *p*-toluenesulfonylamide (1.2 g, 7 mmol), 4Å MS (7 g) and a catalytic amount of Amberlyst 15 in 7 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recrystallization 1.57 g (78% yield) of **78d** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[146] δ = 8.94 (s, 1H), 7.90 – 7.89 (d, *J* = 2.8 Hz, 2H), 7.87 – 7.86 (d, *J* = 2.8 Hz, 2H), 7.34 – 7.32 (d, *J* = 7.8 Hz, 2H), 6.98 – 6.95 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H), 2.43 (s, 3H).

---

[143] Boultwood, T.; Affron, D. P.; Trowbridge, A. D.; Bull, J. A. *J. Org. Chem*. **2013**, *78*, 6632.
[144] Cui, X.**;** Shi, F.; Deng, Y. *Chem. Commun.* **2012**, *48*, 7586.
[145] Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **1999**, *122*, 976.

***N*-(4-trifluoromethylbenzylidene)-4-methylbenzenesulfonamide 78e.**

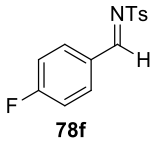


78e

Following the general procedure **B**, 4-trifluoromethylbenzaldehyde (0.93 ml, 7 mmol), *p*-toluenesulfonylamide (1.2 g, 7 mmol), 4Å MS (7 g) and a catalytic amount of Amberlyst 15 in 7 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recrystallization 2.06 g (90% yield) of **78e** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[146] δ = 9.07 (s, 1H), 8.06 – 8.03 (d, *J* = 8.1 Hz, 2H), 7.91 – 7.88 (d, *J* = 8.3 Hz, 2H), 7.76 – 7.73 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.35 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H).

***N*-(4-fluorobenzylidene)-4-methylbenzenesulfonamide 78f.**

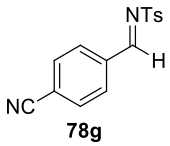


78f

Following the general procedure **B**, 4-fluorobenzaldehyde (0.74 ml, 7 mmol), *p*-toluenesulfonylamide (1.2 g, 7 mmol), 4Å MS (7 g) and a catalytic amount of Amberlyst 15 in 7 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recrystallization 1.55 g (80% yield) of **78f** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[143] δ = 9.00 (s, 1H), 7.98 – 7.93 (dd, *J* = 8.8 and 5.4 Hz, 2H), 7.90 – 7.87 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.33 (d, *J* = 8.2 Hz, 2H), 7.20 – 7.14 (t, *J* = 8.5 Hz, 2H), 2.44 (s, 3H).

***N*-(4-cyanobenzylidene)-4-methylbenzenesulfonamide 78g.**



78g

Following the general procedure **B**, 4-cyanobenzaldehyde (918 mg, 7 mmol), *p*-toluenesulfonylamide (1.2 g, 7 mmol), 4Å MS (7 g) and a catalytic amount of Amberlyst 15 in 7 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recrystallization 636 mg (32% yield) of **78g** were obtained.

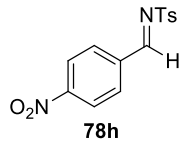
^{1}H NMR (300 MHz, $CDCl_3$):[147] δ = 9.05 (s, 1H), 8.04 – 8.02 (d, *J* = 8.2 Hz, 2H), 7.91 – 7.88 (d, *J* = 8.1 Hz, 2H), 7.79 – 7.76 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.36 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H).

---

[146] a) Love, B. E.; Raje, P. S.; Williams, T. C. *Synlett*, **1994**, 493; b) Chemla, F.; Hebbe, V.; Normant, J. F. *Synthesis* **2000**, 75; c) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976; d) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *14*, 2304.

[147] Barbarotto, M.; Geist, J.; Choppin, S.; Colobert, F. *Tetrahedron: Asymmetry* **2009**, *20*, 2780.

***N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide 78h.**

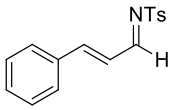


78h

Following the general procedure **B**, 4-nitrobenzaldehyde (1.06 g, 7 mmol), *p*-toluenesulfonylamide (1.2 g, 7 mmol), 4Å MS (7 g) and a catalytic amount of Amberlyst 15 in 7 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recrystallization 404 mg (19% yield) of **78h** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[146] δ = 9.11 (s, 1H), 8.35 – 8.32 (d, *J* = 8.8 Hz, 2H), 8.12 – 8.09 (d, *J* = 8.8 Hz, 2H), 7.92 – 7.89 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.37 (d, *J* = 8.1 Hz, 2H), 2.46 (s, 3H).

4-methyl-*N*-((*E*)-3-phenylallylidene)benzenesulfonamide 79.



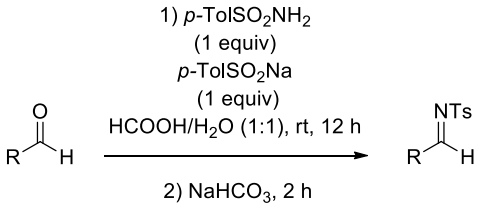
79

Following the general procedure **B**, cinnamaldehyde (1.26 ml, 10 mmol), *p*-toluenesulfonylamide (1.71 g, 10 mmol), 4Å MS (10 g) and a catalytic amount of Amberlyst 15 in 10 ml of toluene were refluxed 18 hours. After filtration through a pad of celite and recrystallization 2.3 g (81% yield) of **79** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[148] δ = 8.78 (d, *J* = 9.4 Hz, 1H), 7.87 – 7.84 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.46 – 7.42 (m, 4H), 7.35 – 7.33 (d, *J* = 8.1 Hz, 2H), 6.99 (dd, *J* = 15.8 and 9.4 Hz, 1H), 2.44 (s, 3H).

General procedure for the synthesis of sulfonyl alkyl imines

GENERAL PROCEDURE C.[57]

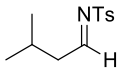


The relevant aldehyde (10.0 mmol, 1.0 equiv) was added to a solution of *p*-toluenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv) and sodium *p*-toluenesulfinate (1.78 g, 10.0 mmol, 1.0 equiv) in formic acid and water (1:1, 30 mL). The mixture was stirred at room temperature for 12 h, then filtered under reduced pressure and washed successively with water (50 mL) and hexane (50 mL). The resulting imine−HO_2STol adduct was dissolved in CH_2Cl_2 (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL) was added. The resulting biphasic solution was vigorously stirred for 2 hours at room temperature. The organic

[148] Yamada, K-I.; Umeki, H.; Maekawa, M.; Yamamoto, Y.; Akindele, T.; Nakano, M.; Tomioka, K. *Tetrahedron* **2008**, *64*, 7258.

layer was separated, dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford the imine, which was sufficiently pure to be further used.

4-methyl-N-(3-methylbutylidene)benzenesulfonamide 80a.

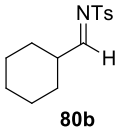


80a

Following the general procedure **C**, butyraldehyde (1.07 ml, 10 mmol), *p*-toluenesulfonylamide (1.71 g, 10 mmol) and sodium *p*-toluenesulfinate (1.78 g, 10.0 mmol) are dissolved in a 1:1 mixture of formic acid (15 ml) and water (15 ml). After treatment with $NaHCO_3$ in CH_2Cl_2 of the resulting imine−HO_2STol adduct, 1.6 g (69% yield) of **80a** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[149] δ = 8.61 – 8.57 (t, *J* = 5.1 Hz, 1H), 7.83 – 7.80 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.32 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H), 2.41 – 2.37 (dd, *J* = 6.9 and 5.1 Hz, 2H), 2.07 (m, 1H), 0.97 – 0.95 (d, *J* = 6.7 Hz, 6H).

***N*-(cyclohexylmethylene)-4-methylbenzenesulfonamide 80b.**

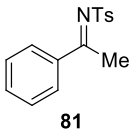


80b

Following the general procedure **C**, cyclohexaldehyde (1.21 ml, 10 mmol), *p*-toluenesulfonylamide (1.71 g, 10 mmol) and sodium *p*toluenesulfinate (1.78 g, 10.0 mmol) are dissolved in a 1:1 mixture of formic acid (15 ml) and water (15 ml). After treatment with $NaHCO_3$ in CH_2Cl_2 of the resulting imine−HO_2STol adduct, 1.3 g (50% yield) of **80b** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$):[146] δ = 8.48 – 8.47 (d, *J* = 4.2 Hz, 1H), 7.80 – 7.77 (d, *J* = 8.1 Hz, 2H), 7.34 – 7.31 (d, *J* = 8.1 Hz, 2H), 2.41 (s, 3H), 1.88 – 1.61 (m, 6H), 1.41 – 1.09 (m, 5H).

4-methyl-*N*-(1-phenylethylidene)benzenesulfonamide 81.



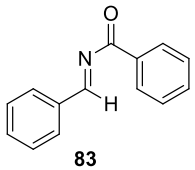
81

Following a reported procedure[58] in a 250 mL round-bottomed flask was charged *p*-toluenesulfinamide (2.33 g, 15 mmol), acetophenone (8.77 mL, 75 mmol), and $Ti(OEt)_4$ (12.58 mL, 60 mmol) in CH_2Cl_2 (120 mL). The mixture was heated at reflux for two days. When the starting material disappeared, MeOH (60 mL) and a few drops of $NaHCO_3$ were added. The insoluble titanium salts were filtered off and the organic layer was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ EtOAc = 7/1) to give 1.35 g (35%) of **81**.

[149] Cui, Z.; Yu, H.-J.; Yang, R.-F.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc*. **2011**, *133*, 12394.

^{1}H NMR (300 MHz, $CDCl_3$): [150] δ = 7.93 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.54-7.35 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.99 (s, 3H), 2.45 (s, 3H).

(*E*)-N-benzylidenebenzamide 83.



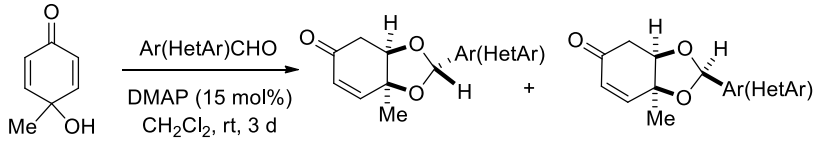
83

Following a reported procedure[59] to a 100 mL flame-dried round bottom flask equipped with stir bar was added 1,1,1,3,3,3-hexamethyldisilazane (5.3 mL, 25.3 mmol) under Argon and cooled to 0 °C. *n*-BuLi (1.6 M in hexanes, 9.62 mL, 24.1 mmol) was added slowly using an air-tight syringe, and the reaction was warmed to room temperature for 15 minutes. The solution was cooled to 0 °C and benzaldehyde (2.33 mL, 23 mmol) was slowly added. The reaction was warmed to room temperature and stirred for 30 minutes. The hexane was rotavaped and the resulting slurry distilled *in vacuo* to give silyl imine **82** (bp 55 °C, 0.2 mm Hg) as a pale yellow liquid (835 mg, 21% yield). Then, it was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. To the solution benzoyl chloride (0.52 ml, 4.5 mmol) was added and the reaction mixture was refluxed for 3 hours. Upon cooling the solvent and TMSCl were removed under reduced pressure to afford the acyl imine **83** as yellow solid (192 mg, 4% yield).

^{1}H NMR (300 MHz, $CDCl_3$):[151] δ = 7.93 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.54-7.35 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.99 (s, 3H), 2.45 (s, 3H).

General procedure for the synthesis of fused acetal derivatives 73/*epi*-73, 84/*epi*-84 and 86/*epi*-86.

GENERAL PROCEDURE D



3

73, **84** and **86**
(major)

***epi*-(73**, **84** and **86)**
(minor)

To a mixture of *p*-quinol **3** (1 equiv) and the corresponding aldehyde or heteroaldehyde (1 equiv) in CH_2Cl_2 (0.5 M) was added DMAP (15 mol%) at room temperature. After 3 days, the mixture was concentrated in vacuo, and the crude mixture was purified by flash column chromatography (eluent indicated in each case).

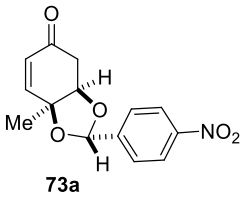
[150] Wolfe, J.; Ney, J. E. *Org. Lett*. **2003**, *5*, 4607.
[151] Breuer, S. W.; Bernath, T.; Ben-Ishai, D. *Tetrahedron,* **1967**, *23*, 2869.

Derivatives 73a-d/*epi*-73a-d

3a,4-Dihydro-7a-methyl-2-(4-nitrophenyl)[*d*][1,3]dioxol-5(7aH)-one (73a/*epi*-73a).

Following general procedure **D**, the reaction of **3** (52 mg, 0.42 mmol) with *p*-nitrobenzaldehyde (75.5 mg, 0.50 mmol) and DMAP (7.6 mg, 0.063 mmol) gave a 90:10 mixture of diastereoisomers **73a/*epi*-73a**, separated after flash chromatography (eluent Hex:AcOEt 3:1): major diastereoisomer **73a** (less polar fraction) 78 mg, 67% yield and minor diastereoisomer ***epi*-73a** (most polar fraction) 4 mg, 3% yield.

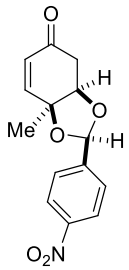
Major diastereoisomer: (2S*,3aR*,7aS*)-73a:



73a

White solid; **M.p.:** 128-130 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.25 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 6.62 (dd, *J* = 10.4 and 2.1 Hz, 1H), 6.18 (dd, *J* = 10.3 and 0.8 Hz, 1H), 5.90 (s, 1H), 4.32 (q, *J* = 2.7 Hz, 1H), 3.02 (ddd, *J* = 17.3, 2.5 and 0.9 Hz, 1H), 2.67 (dd, *J* = 17.1 and 2.9 Hz, 1H), 1.63 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ= 194.8, 148.4, 146.6, 145.0, 130.1, 127.2 (2C), 123.7 (2C), 101.1, 79.3, 78.5, 38.5, 21.2; **MS (EI) m/z (%):** 275 (0.4), 274 (2.2) [M^+-H], 108 (84), 107 (100); **HRMS Calcd for** $C_{14}H_{13}NO_5$ 298.0685, found 298.0680[M^++Na].

Minor diastereoisomer: (2R*,3aR*,7aS*)-*epi*-73a:



***epi*-73a**

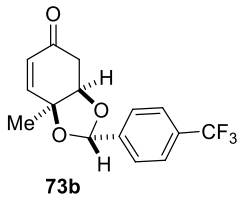
Colorless oil ;**^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.21 (d, *J* = 9.1 Hz, 2H), 7.56 (d, *J* = 9.1 Hz, 2H), 6.50 (dd, *J* = 10.3 and 2.4 Hz, 1H), 6.08 (s, 1H), 5.90 (dd, *J* = 10.3 and 0.7 Hz, 1H), 4.47 (dt, *J* = 3.6 and 2.4 Hz, 1H), 3.07 (ddd, *J* = 17.7, 2.5 and 0.9 Hz, 1H), 2.74 (dd, *J* = 17.8, 3.8 Hz, 1H), 1.60 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 194.2, 149.3 (2C), 144.3, 127.6 (2C), 126.7, 123.6 (2C), 101.7, 81.4 (2C), 37.9, 21.9; **MS (ES) m/z (%):** 298 [M^++Na] (100); **HRMS Calcd for** $C_{14}H_{13}NO_5$ 298.0685, found 298.0682 [M^++Na].

2-(4-Trifluoromethyl)phenyl-3a,4-dihydro-7a-methylbenzo[*d*][1,3]dioxol-5(7aH)-one (73b/*epi*-73b).

Following general procedure **D**, the reaction of **3** (50 mg, 0.40 mmol) with *p*-(trifluoromethyl)benzaldehyde (65 µl, 0.48 mmol) and DMAP (7.2 mg, 0.060 mmol) gave a 80:20 mixture of diastereoisomers **73b/*epi*-73b**, separated after flash chromatography (eluent

Hex:AcOEt 3:1): major diastereoisomer **73b** (less polar fraction) 53 mg, 44% and minor diastereoisomer ***epi*-73b** (most polar fraction) 17 mg, 14 %.

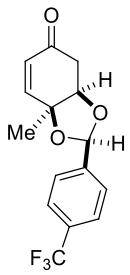
Major diastereoisomer: (2S*,3aR*,7aS*)-73b:



73b

White solid; **M.p.:** 58-60 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.66 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 6.63 (dd, *J* = 10.3, 2.1 Hz, 1H), 6.17 (d, *J* = 10.4 Hz, 1H), 5.88 (s, 1H), 4.32 (q, *J* = 2.6 Hz, 1H), 3.00 (dd, *J* = 17.5 and 0.9 Hz, 1H), 2.65 (dd, *J* = 17.6 and 3.1 Hz, 1H), 1.62 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 194.9, 146.8, 142.1, 131.4, 130.0 (q, *J* = 32.6 Hz), 126.6 (2C), 125.4 (q, *J* = 3.6 Hz, 2C), 123.9 (q, *J* = 272.6 Hz), 101.7, 79.2, 78.3, 38.5, 21.2; **MS (ES) m/z (%):** 299 (27) [M^++H], 321 (100) [M^++Na]; **HRMS Calcd for** $C_{15}H_{13}F_3O_3$ 321.0706, found 321.0709 [M^++Na]$^+$.

Minor diastereoisomer: (2R*,3aR*,7aS*)-*epi*-73b:



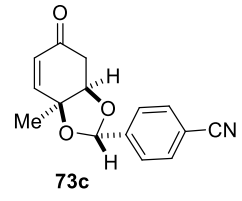
***epi*-73b**

White solid; **M.p.:** 52-54 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.62 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 6.53 (dd, *J* = 10.4 and 2.3 Hz, 1H), 6.06 (s, 1H), 5.93 (d, *J* = 10.4 Hz, 1H), 4.46 (dt, *J* = 3.7 and 2.4 Hz, 1H), 3.07 (ddd, *J* = 17.8, 2.3 and 0.9 Hz, 1H), 2.74 (dd, *J* = 17.8 and 3.8 Hz, 1H), 1.60 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 194.3, 149.5, 141.2, 131.4 (*J* = 32.3 Hz), 130.0, 127.0 (2C), 126.5, 125.3 (*J* = 3.8 Hz, 2C), 123.9 (*J* = 272.9 Hz), 102.2, 81.3, 76.8, 37.9, 21.9; **MS (ES) m/z (%):** 321 (100) [M^++Na], 205 (14.3); HRMS Calcd for $C_{15}H_{13}F_3O_3$ 321.0706, found 321.0709 [M^++Na].

4-(3a,6,7,7a-Tetrahydro-3a-methyl-6-oxobenzo[*d*][1,3]dioxol-2-yl)benzonitrile (73c/*epi*-73c).

Following general procedure **D**, the reaction of **3** (50 mg, 0.40 mmol) with *p*-cyanobenzaldehyde (65 µl, 0.48 mmol) and DMAP (7.2 mg, 0.060 mmol) gave a 80:20 mixture of diastereoisomers **73c/*epi*-73c**, separated after flash chromatography (eluent Hex:AcOEt 3:1): major diastereoisomer **73c** (less polar fraction) 43 mg, 42% yield and minor diastereoisomer ***epi*-73c** (most polar fraction) 18 mg, 18 % yield.

Major diastereoisomer: 4-(2S*,3aS*,7aR*)-73c:

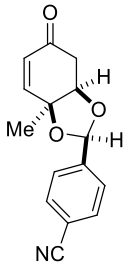


73c

White solid; **M.p.:** 112-114 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.68 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 6.61 (dd, *J* = 10.5 and 2.3 Hz, 1H),

6.17 (d, *J* = 10.5 Hz, 1H), 5.85 (s, 1H), 4.29 (q, *J* = 2.4 Hz, 1H), 2.99 (ddd, *J* = 17.5, 2.6 and 1.1 Hz, 1H), 2.66 (dd, *J* = 17.4 and 3.1 Hz, 1H), 1.61 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ= 194.8, 146.6, 143.2, 132.3 (2C), 130.1, 127.0 (2C), 118.5, 113.1, 101.4, 79.3, 78.5, 38.5, 21.2; **MS (ES) m/z (%):** 256 (100) [M^++H]; **HRMS Calcd for** $C_{15}H_{13}NO_3$ 256.0961, found 256.0968 [M^++H].

Minor diastereoisomer: 4-(2R*,3aS*,7aR*)-*epi*-73c:



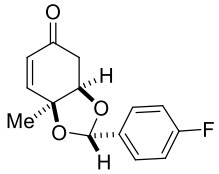
***epi*-73c**

Pale yellow solid; **M.p.:** 98-100 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.65 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 6.50 (dd, *J* = 10.3 and 2.8 Hz, 1H), 6.04 (s, 1H), 5.91 (d, *J* = 10.3 Hz, 1H), 4.46 (dt, *J* = 3.7 and 2.3 Hz, 1H), 3.06 (ddd, *J* = 17.8, 2.4 and 1.0 Hz, 1H), 2.74 (dd, *J* = 17.8, 3.8 Hz, 1H), 1.59 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 194.1, 149.3, 142.4, 132.0 (2C), 127.4 (2C), 118.4, 113.1, 101.9, 81.3, 77.2, 37.9, 21; **MS (ES) m/z (%):** 279 (17.4) 278 (100) [M^++Na], 205 (12); **HRMS Calcd for** $C_{15}H_{13}NO_5$ 278.0780, found 278.0787 [M^++Na].

2-(4-Fluorophenyl)-3a,4-dihydro-7a-methylbenzo[*d*][1,3]dioxol-5(7aH)-one 73d/*epi*-73d.

Following general procedure **D**, the reaction of **3** (20 mg, 0.16 mmol) with *p*-fluorobenzaldehyde (20 µl, 0.19 mmol) and DMAP (2.9 mg, 0.024 mmol) gave a 85:15 mixture of diastereoisomers **73d/*epi*-73d** , separated after flash chromatography (eluent Hex:AcOEt 3:1): major diastereoisomer **73d** (less polar fraction) 21 mg, 53% yield and minor diastereoisomer ***epi*-73d** (most polar fraction) 5 mg, 10 % yield.

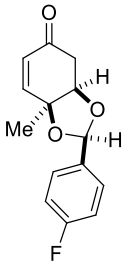
Major diastereoisomer: (2S*,3aR*,7aS*)-73d:



73d

White solid; **M.p.:** 70-72 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.43 (m, 2H), 7.07 (m, 2H), 6.62 (dd, *J* = 10.3 and 2.1 Hz, 1H), 6.17 (dd, *J* = 10.4 and 1.0 Hz, 1H), 5.81 (s, 1H), 4.34 (q, *J* = 2.7 Hz, 1H), 3.00 (ddd, *J* = 17.5, 2.7 and 1.0 Hz, 1H), 2.65 (dd, *J* = 17.4, 3.2 Hz, 1H), 1.62 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ= 195.1, 163.3 (d, *J* = 246 Hz), 146.9, 134.0, 130.1, 128.2 (d, *J* = 8.Hz, 2C), 115.3 (d, *J* = 21.7 Hz, 2C), 102.1, 79.1, 78.0, 38.6, 21.2; **MS (ES) m/z (%):** 271 (100) [M^++Na]; **HRMS Calcd for** $C_{14}H_{13}FO_3$ 271.0740, found 271.0745 [M^++Na].

Minor diastereoisomer: (2R*,3aR*,7aS*)-*epi*-73d:

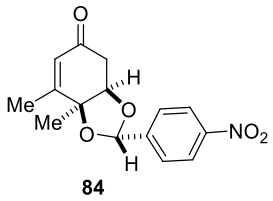

***epi*-73d**

White solid; **M.p.:** 50-52 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.36 (m, 2H), 7.04 (m, 2H), 6.57 (dd, *J* = 10.3 and 2.3 Hz, 1H), 5.99 (s, 1H), 5.97 (dd, *J* = 10.3 and 0.8 Hz, 1H), 4.43 (dt, *J* = 3.8 and 2.3 Hz, 1H), 3.06 (ddd, *J* = 17.7, 2.2 and 0.9 Hz, 1H), 2.74 (dd, *J* = 17.7 and 3.9 Hz, 1H), 1.58 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 193.4, 158.9 (d, *J* = 272 Hz), 148.8, 132.1 (d, *J* = 3.4 Hz), 127.8 (d, *J* = 8.7 Hz, 2C), 125.3, 114.3 (d, *J* = 22.3 Hz, 2C), 101.7, 80.2, 76.2, 36.9, 21.1; **MS (ES) m/z (%):** 271 (100) [M^++Na], 249 (4), 203 (21); **HRMS Calcd for** $C_{14}H_{13}FO_3$ 271.0736, found 271.0740 [M^++Na].

3a,4-Dihydro-7,7a-dimethyl-2-(4-nitrophenyl)benzo[*d*][1,3] dioxol-5(7aH)-one 84/*epi*-84.

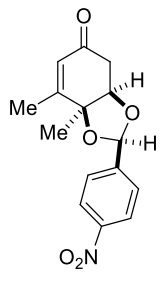
Following general procedure **D**, the reaction of 3-methyl-*p*-quinol **77** (20 mg, 0.14 mmol) with *p*-nitrobenzaldehyde (25.3 mg, 0.50 mmol) and DMAP (3.4 mg, 0.028 mmol) gave a 90:10 mixture of diastereoisomers **84/*epi*-84** , separated after flash chromatography (eluent Hex:AcOEt 3:1): major diastereoisomer **84** (less polar fraction) 27 mg, 67% yield and minor diastereoisomer ***epi*-84** (most polar fraction) 3 mg, 7 % yield.

Major diastereoisomer: (2S*,3aR*,7aS*)-84:


84

White solid; **M.p.:** 82-84 °C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.24 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 6.04 (m, 1H), 5.81 (s, 1H), 4.27 (t, *J* = 2.9 Hz, 1H), 2.98 (ddd, *J* = 17.7, 2.5 and 0.9 Hz, 1H), 2.64 (dd, *J* = 17.1 and 3.3 Hz, 1H), 2.09 (d, *J* = 1.4 Hz, 3H), 1.62 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 194.3, 156.9, 148.5, 145.1, 128.3, 127.2 (2C), 123.6 (2C), 100.8, 80.7, 79.9, 38.1, 20.0, 17.6; **MS (FAB) m/z (%):** 283 (100), 290 [M^++H]; **HRMS Calcd for** $C_{15}H_{15}NO_5$ 290.1028, found 290.1024 [M^++H].

Minor diastereoisomer: (2R*,3aR*,7aS*)-*epi*-84:


***epi*-84**

Colorless oil; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.20 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 6.07 (s, 1H), 5.80 (s, 1H), 4.44 (dd, *J* = 3.5 and 2.3 Hz, 1H), 3.07 (d, *J* = 17.7 Hz, 1H), 2.74 (dd, *J* = 17.7 and 3.8 Hz, 1H), 1.85 (s, 3H), 1.58 (s, 3H); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 193.8, 159.8, 152.6, 144.4, 127.4 (2C), 125.6, 123.6 (2C), 101.7, 82.1, 79.0, 37.6, 20.7, 18.2; **MS (FAB) m/z (%):** 290 [M^++H]; **HRMS Calcd for** $C_{15}H_{15}NO_5$ 290.1028, found 290.1033 [M^++H].

Derivatives 86/*epi*-86

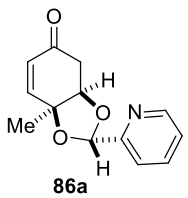
7a-Methyl-2-(2-pyridyl)-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 86a/*epi*-86a.

Following general procedure **D**, the reaction of **3** (100 mg, 0.81 mmol) with 2-pyridine carboxaldehyde **85a** (77 µl, 0.81 mmol) and DMAP (14.8 mg, 0.121 mmol) gave a 73:27 mixture of diastereoisomers **86a/*epi*-86a**. After flash column chromatography (eluent Hex:AcOEt 2:1) major diastereoisomer **86a** (less polar fraction) was obtained as 91:9 mixture of **86a/*epi*-86a** (61 mg, 32%). Minor diastereoisomer ***epi*-86a** (most polar fraction) was obtained as a 50:50 mixture of **86a/*epi*-86a** (15.5 mg, 16%).

Reported procedure using 3 equiv of TMSOTf:[62]

To a stirred solution of pyridine-2-carboxaldehyde **85a** (95 µl, 1 mmol) and *p*-quinol **3** (123 mg, 1 mmol) in acetonitrile (containing 1% H_2O, v/v) (2 mL), was added trimethylsilyl trifluoromethanesulfonate (TMSOTf) (543 µl, 3 mmol,) at 0 °C. After stirring at room temperature for 2 days, the reaction mixture was diluted with diethyl ether (10 mL) and then treated with saturated aqueous K_2CO_3 solution (10 mL). Organic layer was separated and aqueous layer was washed with ether (2 × 5 mL). Combined organic layer was dried over anhydrous sodium sulfate and solvent was evaporated under reduced pressure. The crude product gave a 17:83 mixture of diastereoisomers **86a/*epi*-86a**. After flash column chromatography (eluent Hex:AcOEt 2:1) 76 mg (33% isolated yield) as a mixture of both diastereoisomers was obtained.

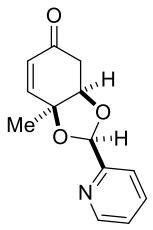
Major diastereoisomer (2*S, 3a*R**, 7a*S**)-86a**:



86a

Colorless oil; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.65 – 8.63 (d, *J* = 4.5 Hz, 1H), 7.79 – 7.74 (td, *J* = 7.7 and 1.8 Hz, 1H), 7.55 – 7.52 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.29 (m, 1H), 6.67 – 6.63 (dd, *J* = 10.3 and 2.2 Hz, 1H), 6.17 – 6.14 (d, 10.5 Hz, 1H), 5.87 (s, 1H), 4.43 (m, 1H), 3.08 – 3.01 (dd, *J* = 17.6 and 2.4 Hz, 1H), 2.69 – 2.62 (dd, *J* = 17.6 and 3.2 Hz, 1H), 1.63 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.0, 156.7, 149.4, 147.0, 136.9, 129.8, 124.0, 120.4, 102.3, 79.3, 78.2, 38.4, 21.1; **MS (EI) *m/z* (%):** 230 (0.13) [M^+-H], 108 (48), 79 (100); **HRMS Calcd for** $C_{13}H_{12}NO_3$ 230.0817, found 230.0822 [M^+-H].

Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-86a**:

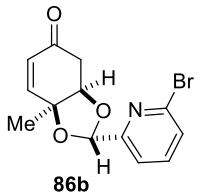

***epi*-86a**

^{1}H NMR (300 MHz, $CDCl_3$) of a 50:50 mixture of **86a/*epi*-86a:** δ = 8.66 - 8.64 (d, *J* = 4.7 Hz, 1H, **86a**), 8.60-8.59 (d, *J* = 4.7 Hz, 1H, ***epi*-86a**), 7.78 – 7.70 (m, 2H, **86a + *epi*-86a**), 7.56-7.53 (d, *J* = 7.8 Hz, 1H, **86a**), 7.46-7.43 (d, *J* = 7.8 Hz, 1H, ***epi*-86a**), 7.31 (m, 2H, **86a + *epi*-86a**), 6.67- 6.63 (dd, *J* = 10.3 and 2.2 Hz, 1H, **86a**), 6.58- 6.54 (dd, *J* = 10.3 and 2.2 Hz, 1H, ***epi*-86a**), 6.18-6.14 (d, *J* = 10.3, Hz, 1H, **86a**), 6.08 (s, 1H, ***epi*-86a**), 5.93-5.90 (d, *J* = 10.3, Hz, 1H, ***epi*-86a**), 5.88 (s, 1H, **86a**) 4.49 – 4.48 (m, 1H, ***epi*-86a**), 4.46 – 4.45 (m, 1H, **86a**), 3.07 (m, 2H, ***epi*-86a + 86a**) 2.78-2.71 (dd, *J* = 17.6 and 3.7 Hz, 1H, ***epi*-86a**), 2.69- 2.62 (dd, *J* = 17.6 and 3.7 Hz, 1H, **86a**), 1.64 (s, 3H, **86a**), 1.60 (s, 3H, ***epi*-86a**); **^{13}C NMR (75 MHz, $CDCl_3$)** of a 50:50 mixture of **86a /*epi*-86a:** δ = 194.9 (**86a**), 194.4 (***epi*-86a**), 156.8 (**86a**), 156.3 (***epi*-86a**), 149.6 (***epi*-86a**), 149.3 (**86a**), 148.8 (***epi*-86a**), 146.9 (**86a**), 136.8 (***epi*-86a**), 136.8 (**86a**), 129.8 (**86a**), 126.3 (***epi*-86a**), 123.9 (**86a**), 123.9 (***epi*-86a**), 120.5 (***epi*-86a**), 120.4 (**86a**), 102.9 (***epi*-86a**), 102.3 (**86a**), 81.1 (***epi*-86a**), 79.2 (**86a**), 78.1 (**86a**), 76.7 (***epi*-86a**), 38.4 (**86a**), 37.8 (***epi*-86a**), 21.8 (***epi*-86a**), 21.0 (**86a**); **MS (EI) *m/z* (%) (86a)**: 230 (0.15) [M^+-H], 108 (48), 79 (100); **HRMS Calcd for** $C_{13}H_{12}NO_3$ 230.0817, found 230.0821 [M^+-H].

2-[(6-Bromo)-2-pyridyl]-7a-methyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 86b/*epi*-86b.

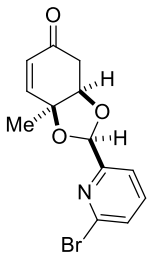
Following general procedure **D**, the reaction of **3** (190 mg, 1.53 mmol) with 6-bromo-2-pyridinecarboxaldehyde **85b** (285 mg, 1.53 mmol) and DMAP (28 mg, 0.23 mmol) gave a 70:30 mixture of diastereoisomers **86b/*epi*-86b**, separated after flash column chromatography (eluent Hex:AcOEt 2:1): minor diastereoisomer ***epi*-86b** (less polar fraction) 52 mg, 11% yield and major diastereoisomer **86b** (most polar fraction) 143 mg, 30% yield.

Major diastereoisomer (2*S, 3a*R**, 7a*S**)-86b**:


86b

White solid; **M.p.:** 87 - 89 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.63 – 7.58 (m, 2H), 7.50 (s, 1H), 7.47 (s, 1H), 6.64 – 6.60 (dd, *J* = 10.3 and 2.1 Hz, 1H), 6.16 – 6.12 (dd, *J* = 10.3 and 2.1 Hz, 1H), 5.81 (s, 1H), 4.42 – 4.40 (q, *J* = 2.7 Hz, 1H), 3.06 – 2.99 (ddd, *J* = 17.6, 2.7 and 1.1 Hz, 1H), 2.68 – 2.61 (dd, *J* = 17.6 and 3.0 Hz, 1H), 1.62 (s, 3H): **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.7, 158.4, 146.8, 141.9, 139.1, 129.9, 128.6, 119.2, 101.7, 79.5, 78.4, 38.4, 21.2; **MS (ESI) *m/z* (%):** 310 (100) [M^++H], 334 (39), 312 (97); **HRMS Calcd for** $C_{13}H_{13}NO_3Br$ 310.0073, found 310.0081 [M^++H].

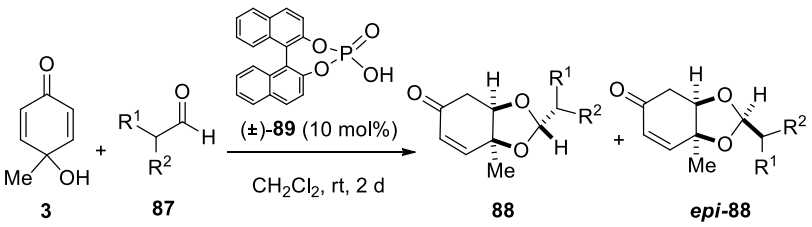
Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-86b**:


***epi*-86b**

White solid; **M.p.:** 91 - 93 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.58 – 7.50 (m, 1H), 7.47 – 7.45 (m, 1H) 7.39 – 7.3 (d, *J* = 7.4 Hz, 1H), 6.57 – 6.52 (dd, *J* = 10.3 and 2.3 Hz, 1H), 5.98 (s, 1H), 5.94 – 5.90 (d, *J* = 10.4 Hz, 1H), 4.47 – 4.4 (m, 1H), 3.11 – 3.05 (dd, *J* = 17.1 and 2.3 Hz, 1H), 2.77 – 2.70 (dd, *J* = 17.7 and 3.7 Hz, 1H), 1.59 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.3, 157.8, 149.5, 141.4, 139.1, 128.6, 126.6, 119.5, 102.2, 77.0, 81.3, 37.9, 21.9; **MS (EI) *m/z* (%):** 156(100), 158 (94), 309 (0.73) [M^+-H]; **HRMS Calcd for** $C_{13}H_{13}NO_3Br$ 309.0001, found 309.0004 [M^+-H].

General procedures for the synthesis of bicyclic acetal derivatives 88

GENERAL PROCEDURE E



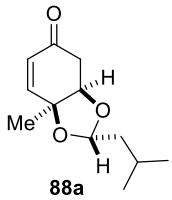
To a mixture of *p*-quinol **3** (1 equiv) and the aliphatic aldehyde **87** (1.1 equiv) in CH_2Cl_2 (0.1 M) was added the corresponding aryl phosphoric acid **(±)-89** (10 mol%) at room temperature. After 2 days, the mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (eluent indicated in each case).

Derivatives 88a-*g*

2-(*iso*Butyl)-7a-methyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 88a/*epi*-88a.

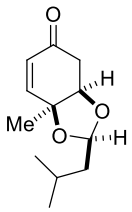
Following general procedure **E**, the reaction of **3** (70 mg, 0.56 mmol) with 3-methylbutanal **87a** (66.5 µl, 0.62 mmol) and phosphoric acid **(±)-89** (19 mg, 0.056 mmol) gave a 76:24 mixture of diastereoisomers **88a/*epi*-88a**, separated after flash column chromatography (eluent Hex:AcOEt 7:1): major diastereoisomer **88a** (less polar fraction) 77.5 mg, 65% yield and minor diastereoisomer ***epi*-88a** (most polar fraction) 27 mg, 23% yield.

Major diastereoisomer (2*S, 3a*R**, 7a*S**)-88a**:


88a

White solid; **M.p.:** 102-104 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.51 – 6.47 (dd, *J* = 10.2 and 2.2 Hz, 1H), 6.09 – 6.05 (d, *J* =10.2 Hz, 1H), 4.97 (t, *J* = 5.1 Hz, 1H), 4.16 (m, 1H), 2.94 – 2.87 (ddd, *J* = 17.5, 2.5 and 1.0 Hz, 1H), 2.60 – 2.53 (dd, *J* = 17.5 and 3.2 Hz, 1H), 1.84-1.71 (m, 1H), 1.52 (m, 2H), 1.51 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.7, 147.7, 129.8, 102.9, 78.3, 77.0, 43.8, 38.9, 24.2, 22.9 (2C), 21.4; **MS (EI) *m/z* (%):** 209 (1.02) [M^+-H], 79 (60), 153 (81), 125 (100); **HRMS Calcd for** $C_{12}H_{17}O_3$ 209.1178, found 209.1179 [M^+-H].

Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-88a**:

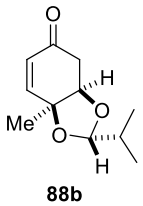

***epi*-88a**

Colorless oil; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.53 – 6.49 (dd, *J* = 10.3 and 2.4 Hz, 1H), 5.90– 5.87 (d, *J* = 10.3 Hz, 1H), 5.17 (t, *J* = 5.2 Hz, 1H), 4.19 (m, 1H), 2.97– 2.90 (ddd, *J* = 17.8, 2.5 and 1.0 Hz, 1H), 2.66 – 2.59 (dd, 17.8 and 3.7 Hz, 1H), 1.62 -1.78 (m, 1H), 1.51 (m, 2H), 1.47 (s, 3H), 0.92 (s, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.9, 150.4, 125.9, 103.4, 80.4, 75.6, 43.7, 38.0, 24.2, 22.9, 22.8, 21.9; **MS (EI) *m/z* (%):** 209 (0.9) [M^+-H], 79 (60), 153 (83), 125 (100); **HRMS Calcd for** $C_{12}H_{17}O_3$ 209.1178, found 209.1178 [M^+-H].

2-(*iso*Propyl)-7a-methyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 88b/*epi*-88b.

Following general procedure **E**, the reaction of **3** (70 mg, 0.56 mmol) with 2-methylpropanal **87b** (57 µl, 0.62 mmol) and phosphoric acid (**±)-89** (19 mg, 0.056 mmol) gave a 89:11 mixture of diastereoisomers **88b/*epi*-88b**. After flash column chromatography (eluent Hex:AcOEt 7:1) major diastereoisomer **88b** (less polar fraction) was obtained pure (91.7 mg, 83% yield) and minor diastereoisomer ***epi*-88b** (most polar fraction) as a 80:20 mixture of ***epi*-92b/92b** (4.5 mg, 4% yield).

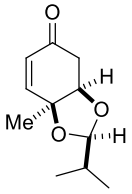
Major diastereoisomer (2*S, 3a*R**, 7a*S**)-88b**:


88b

White solid; **M.p.:** 57-59 °C; **^{1}H NMR (300 MHz, $CDCl_3$) :** δ = 6.52 – 6.48 (dd, *J* = 10.3 and 2.2 Hz, 1H), 6.08 – 6.04 (d, *J* = 10.3 Hz, 1H), 4.70– 4.69 (d, *J* = 4.1 Hz, 1H), 4.09 – 4.06 (q, *J* = 2.7 Hz, 1H), 2.95 – 2.88(ddd, *J* = 17.5, 2.5 and 0.9 Hz, 1H), 2.58 – 2.51 (dd, *J* = 17.5 and 3.1 Hz, 1H), 1.87 – 1.71 (m, 1H), 1.50 (s, 3H), 0.93 - 0.90 (dd, *J* = 6.8 and 1.4 Hz, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.7, 147.7, 129.7, 107.1, 78.8,

77.0, 38.8, 32.6, 21.0, 16.4, 16.2; **MS (EI) *m/z* (%):** 195 (0.89) [M^+-H], 196 (0.1) [M^+], 153 (98), 125 (100); **HRMS Calcd for** $C_{11}H_{15}O_3$ 195.1021, found 195.1030 [M^+-H].

Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-88b:**

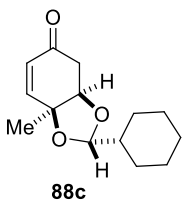

***epi*-88b**

^{1}H NMR (300 MHz, $CDCl_3$) of a 80:20 mixture of **88b/*epi*-88b:** δ = 6.52 – 6.47 (dd, *J* = 10.3 and 2.4 Hz, 1H (***epi*-88b**) + 0.25H (**88b**)), 6.08 – 6.04 (dd, *J* = 10.3 and 1.1 Hz, 0.25H (**88b**)), 5.90 – 5.86 (dd, *J* = 10.3 and 1.0 Hz, 1H (***epi*-88b**)), 4.87 – 4.85 (d, *J* = 4.7 Hz, 1H **(*epi*-88b**)), 4.70 – 4.69 (d, *J* = 4.2 Hz, 0.25H (**88b**)), 4.21 – 4.18 (m, 1H (***epi*-88b**)), 4.09 – 4.06 (q, *J* = 2.7 Hz, 0.25H (**88b**)), 2.98 – 2.91(ddd, *J* = 17.7, 2.3 and 0.8 Hz, 1H (***epi*-88b**)), 2.95 – 2.88 (ddd, *J* = 17.7, 2.7 and 1.0 Hz, 0.25H (**88b**)), 2.67 – 2.59 (dd, *J* = 17.7 and 3.8, 1H (***epi*-88b**)), 2.58 – 2.5 (dd, *J* = 17.4 and 3.1, 0.25H (**88b**)), 1.84 – 1.69 (m, 1H (***epi*-88b**) + 0.25H (**88b**)), 1.50 (s, 0.75H (**88b**)), 1.48 (s, 3H (***epi*-88b**)), 0.93 – 0.86 (m, 6H (***epi*-88b**) + 1.5H (**88b**)); **^{13}C NMR (75 MHz, $CDCl_3$)** of a 80:20 mixture of **88b/*epi*-88b:** δ = 195.7 (**88b**) , 194.9 (***epi*-88b**), 150.4 (***epi*-88b**), 147.8 (**88b**), 129.7 (**88b**), 125.9 (***epi*-88b**), 107.7 (***epi*-88b**), 107.2 (**88b**), 80.4 (***epi*-88b**), 78.8 (**88b**), 75.6 (***epi*-88b**), 38.8 (**88b**), 37.9 (***epi*-88b**), 32.7 (**88b**), 32.2 (***epi*-88b**), 22.1 (***epi*-88b**), 21.1 (**88b**), 16.8 (***epi*-88b**), 16.7 (***epi*-88b**), 16.4 (**88b**), 16.3 (**88b**); **MS (EI) *m/z* (%):** 195 (0.92) [M^+-H], 196 (0.1) [M^+], 153 (95), 125 (100); **HRMS Calcd for** $C_{11}H_{15}O_3$ 195.1019, found 195.1027 [M^+-H].

2-(Cyclohexyl)-7a-methyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 88c/*epi*-88c.

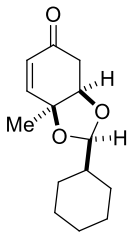
Following general procedure **E**, the reaction of **3** (70 mg, 0.56 mmol) with cyclohexanecarboxaldehyde **87c** (75 µl, 0.62 mmol) and phosphoric acid (**±)-89** (19 mg, 0.056 mmol) gave a 83:17 mixture of diastereoisomers **88c/*epi*-88c**, separated after flash column chromatography (eluent Hex:AcOEt 7:1): major diastereoisomer **88c** (less polar fraction) 107.8 mg, 81% yield and minor diastereoisomer ***epi*-88c** (most polar fraction) 21.3 mg, 16% yield.

Major diastereoisomer (2*S, 3a*R**, 7a*S**)-88c**:


88c

White solid; **M.p.:** 102-104 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.51-6.47 (dd, *J* = 10.3 and 2.2 Hz, 1H), 6.06 – 6.03 (dd, *J* = 10.2 and 1.1 Hz, 1H), 4.68 - 4.66 (d, *J* = 4.3 Hz, 1H), 4.06 - 4.03 (m, 1H), 2.94 – 2.87 (ddd, *J* = 17.5, 2.7 and 1.1 Hz, 1H), 2.57 – 2.51 (dd, *J* = 17.5 and 3.2 Hz, 1H), 1.72 (m, 6H), 1.49 (s, 3H), 1.18 (m, 5H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.7, 147.8, 129.7, 106.6, 78.7, 77.0, 42.4, 38.8, 26.9, 26.7, 26.4, 25.7, 25.7, 21.0; **MS (EI) *m/z* (%):** 235 (0.50) [M^+-H], 236 (0.1) [M^+], 125 (75), 153 (100); **HRMS Calcd for** $C_{14}H_{19}O_3$ 235.1334, found 235.1342 [M^+-H].

Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-88c**:

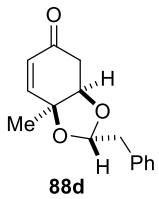

***epi*-88c**

Colorless oil; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.51 – 6.48 (d, *J* = 10.9 Hz, 1H), 5.90 – 5.86 (d, *J* = 10.3 Hz, 1H), 4.86 – 4.85 (d, *J* = 4.7 Hz, 1H), 4.18 (m, 1H), 2.97 – 2.91 (d, *J* = 17.7 Hz, 1H), 2.67 – 2.60 (dd, *J* = 17.5 and 3.7 Hz, 1H), 1.70 (m, 6H), 1.47 (s, 3H), 1.15 (s, 5H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.0, 150.5, 125.9, 106.9, 80.3, 75.5, 41.8, 37.9, 27.2, 26.9, 26.3, 25.7, 25.6, 22.1; **MS (EI) *m/z* (%):** 235 (0.7) [M^+-H], 236 (0.1) [M^+], 125 (99), 153 (100); **HRMS Calcd for** $C_{14}H_{19}O_3$ 235.1334, found 235.1338 [M^+-H].

2-(Benzyl)-7a-methyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 88d/*epi*-88d.

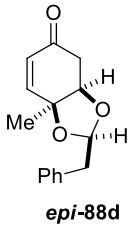
Following general procedure **E**, the reaction of **3** (70 mg, 0.56 mmol) with phenylacetaldehyde **87d** (72.6 µl, 0.62 mmol) and phosphoric acid (**±**)**-89** (19 mg, 0.056 mmol) gave a 87:13 mixture of diastereoisomers **88d/*epi*-88d**, separated after flash column chromatography (eluent Hex:AcOEt 6:1): major diastereoisomer **88d** (less polar fraction) 117.5 mg, 86% yield and minor diastereoisomer ***epi*-88d** (most polar fraction) 11 mg, 8% yield.

Major diastereoisomer (2*S, 3a*R**, 7a*S**)-88d**:


88d

Colorless oil; **^{1}H NMR (300 MHz,$CDCl_3$):** δ = 7.27 (m, 5H), 6.49 – 6.45 (dd, *J* = 10.3 and 2.2 Hz, 1H), 6.04 – 6.0 (d, *J* = 10.3 Hz, 1H), 5.18 (t, *J* = 4.2 Hz, 1H), 3.89 – 3.86 (q, *J* = 2.7 Hz, 1H), 2.94 – 2.93 (d, *J* = 4.2 Hz, 2H), 2.90 – 2.83 (ddd, *J* = 17.5, 2.8 and 1.1 Hz, 1H), 2.53 – 2.46 (dd, *J* = 17.5 and 3.2 Hz, 1H), 1.43 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.4, 147.6, 135.4, 130.0 (2C), 129.4, 128.1 (2C), 126.6, 103.4, 78.5, 77.0, 41.5, 38.5, 21.00; **MS (EI) *m/z* (%):** 243 (0.4) [M^+-H], 125 (83), 153 (91), 91 (100); **HRMS Calcd for** $C_{15}H_{15}O_3$ 243.1021, found 243.1021 [M^+-H].

Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-88d:**

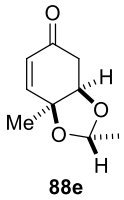

***epi*-88d**

Colorless oil; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.25 (m, 5H), 6.37 – 6.33 (dd, *J* = 10.3 and 2.4 Hz, 1H), 5.72 – 5.68 (d, *J* = 10.3, 1H), 5.34 – 5.31 (t, *J* = 4.5 Hz, 1H), 4.20 – 4.18 (m, 1H), 2.97 – 2.88 (m, 3H), 2.63 – 2.53 (dd, *J* = 17.7 and 3.8 Hz, 1H), 1.45 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 194.8, 149.7, 135.2, 130.1 (2C), 128.2 (2C), 126.7, 125.8, 103.88, 80.58, 76.1, 41.4, 37.9, 21.9; **MS (EI) *m/z* (%):** 243 (0.3) [M^+-H], 236 (0.1) [M^+], 125 (86), 153 (96), 91 (100); **HRMS Calcd for** $C_{15}H_{15}O_3$ 243.1021, found 243.1010 [M^+-H].

2,7a-Dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 88e/*epi*-88e.

Following general procedure **E**, the reaction of **3** (70 mg, 0.56 mmol) with acetaldehyde **87e** (35 µl, 0.62 mmol) and phosphoric acid (**±)-89** (19 mg, 0.056 mmol) gave a 67:33 mixture of diastereoisomers **88e/*epi*-88e**. After flash column chromatography (eluent Hex:AcOEt 7:1) major diastereoisomer **88e** (less polar fraction) was obtained pure (38.8 mg, 41% yield) whereas minor diastereoisomer ***epi*-88e** was not observed after purification (10% yield calculated from the ^{1}H-NMR spectrum of the mixture).

Major diastereoisomer: (2*S, 3a*R**, 7a*S**)-88e**:



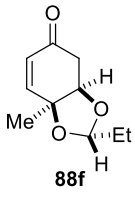
88e

Colorless oil; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.50 – 6.46 (dd, *J* = 10.3 and 2.2 Hz, 1H), 6.08 – 6.05 (d, *J* = 10.4 Hz, 1H), 5.09 – 5.04 (q, *J* = 4.9 Hz, 1H), 4.18 – 4.15 (q, *J* = 2.7 Hz, 1H), 2.92 – 2.85 (ddd, *J* = 17.5, 2.5 and 1.2 Hz, 1H), 2.60 – 2.53 (dd, *J* = 17.5 and 3.2 Hz, 1H), 1.51 (s, 3H), 1.35 – 1.33 (d, *J* = 4.9 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.5, 147.4, 129.8, 100.7, 78.4, 77.0, 38.8, 21.3, 20.9; **MS (EI) *m/z* (%):** 167 (7) [M^+-H], 79 (78), 125 (91), 153 (100); **HRMS Calcd for** $C_9H_{11}O_3$ 167.0708, found 167.0701 [M^+-H].

2-(Ethyl)-7a-methyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 88f/*epi*-88f.

Following general procedure **E**, the reaction of **3** (70 mg, 0.56 mmol) with propionaldehyde **87f** (45 µl, 0.62 mmol) and phosphoric acid (**±)-89** (19 mg, 0.056 mmol) gave a 76:24 mixture of diastereoisomers **88f/*epi*-88f**, separated after flash column chromatography (eluent Hex:AcOEt 7:1): major diastereoisomer **88f** (less polar fraction) 51.3 mg, 50% yield and minor diastereoisomer ***epi*-88f** (most polar fraction) 15 mg, 15% yield.

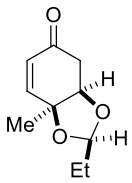
Major diastereoisomer (2*S, 3a*R**, 7a*S**)-88f**:



88f

Colorless oil; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.52 – 6.48 (dd, *J* = 10.3 and 2.2 Hz, 1H), 6.08 – 6.05 (d, *J* = 10.3 Hz, 1H), 4.92 – 4.87 (t, *J* = 4.5 Hz, 1H), 4.14 – 4.11 (q, *J* = 2.7 Hz, 1H), 2.95 – 2.88 (ddd, *J* = 17.5, 2.8 and 0.8, 1H), 2.60 – 2.53 (dd, *J* = 17.5 and 3.2, 1H), 1.69 – 1.57 (m, 2H), 1.51 (s, 3H), 0.95 – 0.90 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.6, 147.6, 129.8, 104.4, 78.6, 77.0, 38.8, 27.9, 21.2, 7.5; **MS (EI) *m/z* (%):** 181 (1.6) [M^+-H], 125 (84), 153 (100); **HRMS Calcd for** $C_{10}H_{13}O_3$ 181.0865, found 181.0858 [M^+-H].

Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-88f:**



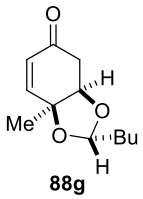
***epi*-88f**

Colorless oil; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.53 – 6.49 (dd, *J* = 10.2 and 2.6 Hz, 1H), 5.90 – 5.87 (d, *J* = 10.5 Hz, 1H), 5.11 – 5.08 (t, *J* = 4.6 Hz, 1H), 4.22 – 4.19 (m, 1H), 2.98 – 2.91 (dd, *J* = 17.8 and 1.8 Hz, 1H), 2.67 – 2.60 (dd, *J* = 17.7 and 3.9 Hz, 1H), 1.62– 1.51 (m, 2H), 1.48 (s, 3H), 0.91 – 0.86 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.9, 150.3, 125.9, 104.9, 80.4, 75.7, 37.9, 27.6, 21.9, 7.7; **MS (EI) *m/z* (%):** 181 (1.6) [M^+-H], 125 (84), 153 (100); **HRMS Calcd for** $C_{10}H_{13}O_3$ 181.0865, found 181.0860 [M^+-H].

2-(Butyl)-7a-methyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one 88g/*epi*-88g.

Following general procedure **E**, the reaction of **3** (70 mg, 0.56 mmol) with pentanal **87g** (66 µl, 0.62 mmol) and phosphoric acid (**±**)-**89** (19 mg, 0.056 mmol) gave a 76:24 mixture of diastereoisomers **88g/*epi*-88g**, separated after flash column chromatography (eluent Hex:AcOEt 7:1): major diastereoisomer **88g** (less polar fraction) 88.8 mg, 75% yield and minor diastereoisomer ***epi*-88g** (most polar fraction) 23.7 mg, 20% yield.

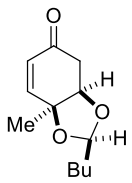
Major diastereoisomer (2*S,3a*R**,7a*S**)-88g**:



88g

White solid; **M.p.:** 42-44 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.5 – 6.46 (dd, *J* = 10.4 and 2.1 Hz, 1H), 6.07 – 6.04 (d, *J* = 10.3 Hz, 1H), 4.94 – 4.91 (t, *J* = 4.7 Hz, 1H), 4.13 – 4.10 (q, *J* = 2.7 Hz, 1H), 2.93 – 2.86 (ddd, *J* = 17.4, 2.8 and 1.2 Hz, 1H), 2.59 – 2.52 (dd, *J* = 17.5 and 3.2 Hz, 1H), 1.63 – 1.58 (m, 2H), 1.50 (s, 3H), 1.38 – 1.32 (m, 4H), 0.91 – 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.6, 147.6, 129.8, 103.7, 78.4, 77.0, 38.8, 34.6, 25.6, 22.5, 21.2, 13.9; **MS (EI) *m/z* (%):** 209 (2) [M^+-H], 107 (58), 153 (99), 125 (100); **HRMS Calcd for** $C_{12}H_{17}O_3$ 209.1178, found 209.1174 [M^+-H].

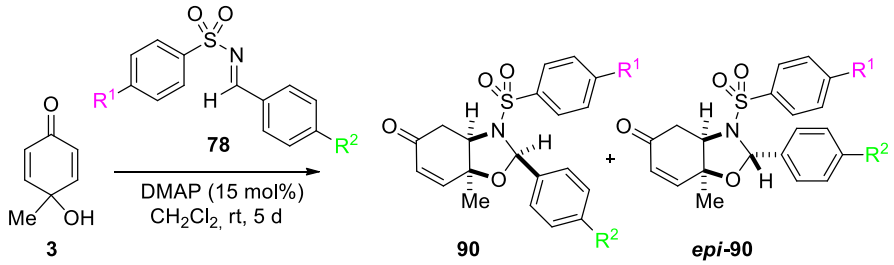
Minor diastereoisomer (2*R, 3a*R**, 7a*S**)-*epi*-88g**:



***epi*-88g**

White solid; **M.p.:** 45-47 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.53 – 6.49 (dd, *J* = 10.3 and 2.4 Hz, 1H), 5.91 – 5.87 (d, *J* = 10.4 Hz, 1H), 5.14 – 5.11 (t, *J* = 4.8 Hz, 1H), 4.20 (m, 1H), 2.98 – 2.91 (ddd, *J* = 17.8, 2.3 and 0.8 Hz, 1H), 2.67 – 2.60 (dd *J* = 17.7 and 3.7 Hz, 1H) 1.54 (m, 5H), 1.35 – 1.26 (m, 4H), 0.90 – 0.85 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 194.9, 150.4, 125.9, 104.3, 80.4, 75.7, 37.9, 34.4, 25.8, 22.5, 21.9, 13.9; **MS (EI) *m/z* (%):** 209 (2) [M^+-H], 107 (54), 125 (99), 153 (100); HRMS Calcd for $C_{12}H_{17}O_3$ 209.1178, found 209.1180 [M^+-H].

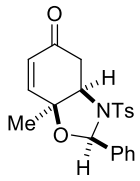
GENERAL PROCEDURE F



To a mixture of *p*-quinol **3** (1 equiv) and the corresponding arylsulfonyl aryl aldimine **78** (1 equiv) in CH_2Cl_2 (0.5 M) was added DMAP (15 mol%) at room temperature. After 5 days the crude mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (eluent indicated in each case).

Bicyclic N,O-acetals 90a,e-h

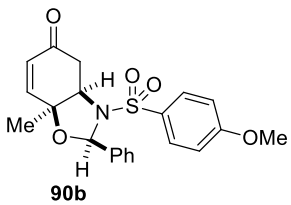
Bicyclic N,O-Acetal 90a.


90a

Following general procedure **F**, the reaction of **3** (57 mg, 0.46 mmol) with aryl imine **78a** (115 mg, 0.46 mmol) and DMAP (8.4 mg, 0.069 mmol) gave compound **90a** as the unique diastereoisomer. Purification by flash column chromatography (eluent Hex:AcOEt 2:1) gave 88 mg of **90a** (50% yield).

White solid; **M.p.:** 153-155 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.71 – 7.68 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.39 (m, 2H), 7.36 – 7.32 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.25 (m, 3H), 6.19 – 6.15 (dd, *J* = 10.4 and 1.2 Hz, 1H), 6.14 (s, 1H), 5.63 – 5.59 (dd, *J* = 10.4 and 0.8 Hz, 1H), 3.96 – 3.92 (m, 1H), 3.33 – 3.26 (ddd, *J* = 17.1, 4.1 and 0.9 Hz, 1H), 2.69 – 2.62 (dd, *J* = 17.1 and 4.8 Hz, 1H), 2.44 (s, 3H), 1.30 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.9, 148.6, 144.7, 138.6, 133.3, 129.9 (2C), 128.7, 128.6, 128.1 (2C), 128.1 (2C), 127.2 (2C), 91.1, 78.9, 63.6, 39.9, 23.4, 21.6; **MS (ESI) *m/z* (%):** 384 (12) [M^++H], 278 (94), 406 (100) [M^++Na]; **HRMS Calcd for** $C_{21}H_{22}NO_4S$ 384.1264, found 384.1264 [M^++H].

Bicyclic N,O-Acetal 90b.


90b

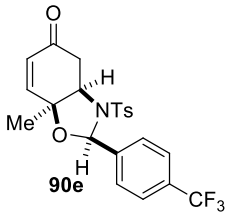
Following general procedure **F**, the reaction of **3** (218 mg, 1.75 mmol) with aryl imine **78b** (483 mg, 1.75 mmol) and DMAP (32 mg, 0.26 mmol) gave compound **90b** as the unique diastereoisomer. Purification by flash column chromatography (eluent Hex:AcOEt 2:1) gave 304 mg of **90b** (75% yield).

White solid; **M.p.:** 153-156 °C; **^{1}H NMR (300 MHz,$CDCl_3$):** δ = 7.76 – 7.73 (d, *J* = 8.9 Hz, 2H), 7.42 – 7.49 (m, 2H), 7.29 – 7.26 (m, 3H), 7.01 – 6.98 (d, *J* = 8.9 Hz, 2H), 6.21 – 6.17 (dd, *J* = 10.4 and 1.2 Hz, 1H), 6.15 (s, 1H), 5.64 – 5.61 (d, *J* = 10.3 Hz, 1H), 3.97 – 3.94 (m, 1H), 3.89 (s, 3H), 3.33 – 3.23 (dd, *J* = 17.1 and 4.1 Hz, 1H), 2.69 – 2.62 (dd, *J* = 17.1 and 4.8 Hz, 1H), 1.34 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.9, 163.5, 148.6, 138.7, 130.1 (2C), 128.4, 128.3, 127.8 (2C), 127.1, 126.9 (2C), 114.4 (2C), 90.7, 78.8, 63.5, 55.5, 39.7, 23.1; **MS (EI) *m/z* (%):** 399 (0.04) [M^+], 275 (36), 171 (100) [M^++Na]; **HRMS Calcd for** $C_{21}H_{21}NO_5S$ 399.1140, found 399.1154 [M^+].

Bicyclic N,O-Acetal 90e/*epi*-90e.

Following general procedure **F**, the reaction of **3** (96 mg, 0.78 mmol) with aryl imine **78e** (254 mg, 0.78 mmol) and DMAP (14 mg, 0.116 mmol) gave a 76:24 mixture of diastereoisomers **90e/*epi*-90e**. After flash column chromatography (eluent Hex:AcOEt 2:1) major diastereoisomer **90e** (less polar fraction) was obtained pure (159 mg, 46% yield) and minor diastereoisomer ***epi*-90e** (most polar fraction) contains a 80:20 mixture of **90e/*epi*-90e** (12 mg, 4% yield).

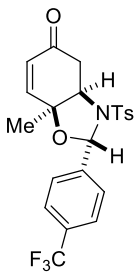
Major diastereoisomer (2*R, 3a*R**, 7a*S**)-90e**:



90e

White solid; **M.p.:** 205-207 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.73 – 7.70 (d, *J* = 8.3 Hz, 2H), 7.55 (s, 4H), 7.38 – 7.36 (d, *J* = 7.9 Hz, 2H), 6.15 (s, 1H), 6.15 – 6.11 (d, *J* = 10.2 Hz, 1H), 5.63 – 5.59 (d, *J* = 10.3 Hz, 1H), 3.94 – 3.91 (m, 1H), 3.37 – 3.30 (dd, *J* = 17.2 and 3.7 Hz, 1H), 2.70 – 2.62 (dd, *J* = 17.2 and 4.6 Hz, 1H), 2.47 (s, 3H), 1.34 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.6, 148.4, 145.1, 142.9, 132.3, 131.2 – 129.9 (q, *J* = 32.4Hz), 130.1 (2C), 129.0, 128.2 (2C), 127.5 (2C), 125.1 - 124.9 (q, *J* = 3.6 Hz, 2C), 90.2, 79.5, 63.9, 39.6, 23.2, 21.6; **^{19}F NMR (282.4 MHz, $CDCl_3$):** δ = -62.55; **MS (EI) *m/z* (%):** 450 (0.1) [M^+-H], 145 (50), 155 (98), 91 (100); **HRMS Calcd for** $C_{22}H_{19}NO_4F_3S$ 450.0987, found 450.1009 [M^+-H].

Minor diastereoisomer (2*S, 3a*R**, 7a*S**)-*epi*-90e**:



***epi*-90e**

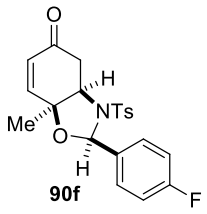
^{1}H NMR (300 MHz, $CDCl_3$) of a 80:20 mixture of **90e/*epi*-90e:** δ = 7.73 – 7.70 (d, *J* = 8.3 Hz, 2H, (**90e**)), 7.55 (s, 4H, (**90e**)), 7.44 – 7.41 (d, *J* = 8.0 Hz, 1H, (***epi*-90e**)) 7.38 – 7.35 (d, *J* = 8.3 Hz, 2H, (**90e**)), 7.32 – 7.30 (d, *J* = 8.0 Hz, 1H, (***epi*-90e**)), 7.01 – 6.93 (m, 1H, (***epi*-90e**)), 6.62 – 6.58 (dd, *J* = 10.3 and 1.9 Hz, 0.25H, (***epi*-90e**)), 6.14 (s, 1H, (**90e**)) 6.14 – 6.10 (d, *J* = 10.7 Hz, 1H, (**90e**)), 5.93 (s, 0.25H, (***epi*-90e**)), 5.61 – 5.58 (d, *J* = 10.3 Hz, 1H, (**90e**)), 4.07 – 4.05 (m, 0.25H, (***epi*-

90e)), 3.93 – 3.89 (m, 1H, (**90e**)), 3.65 – 3.58 (dd, *J* = 17.3 and 3.2 Hz, 0.25H, (***epi*-90e**)), 3.37 – 3.30 (dd, *J* = 17.1 and 3.7 Hz, 1H, (**90e**)), 2.73 – 2.66 (dd, *J* = 18.0 and 3.6 Hz, 0.25H, (***epi*-90e**)), 2.70 – 2.62 (dd, *J* = 17.1 and 4.6 Hz, 1H, (**90e**)), 2.46 (s, 3H, (**90e**)), 2.33 (s, 0.75H, (***epi*-90e**)), 1.63 (s, 0.75H, (***epi*-90e**)), 1.32 (s, 3H, (**90e**)); **^{13}C NMR-*epi*-94e (75 MHz, $CDCl_3$):** δ = 193.4, 147.3, 143.4, 136.9, 130.8, 130.4, 130.2, 129.3 (2C), 129.2 (2C), 126.3 (2C), 125.7, 124.9 - 124.7 (q, *J* = 3.4 Hz) 122.1, 90.5, 79.9, 62.7, 37.6, 22.1, 21.3; **^{19}F NMR (282.4 MHz, $CDCl_3$)** of a 80:20 mixture of **90e/*epi*-90e:** δ = -62.62 (**90e**), -62.78 (***epi*-90e**); **MS (EI) *m/z* (%):** 450 (0.1) [M^+-H], 145 (50), 155 (98), 91 (100); **HRMS Calcd for** $C_{22}H_{19}NO_4F_3S$ 450.0987, found 450.1002 [M^+-H].

Bicyclic N,O-Acetal 90f/*epi*-90f.

Following general procedure **F**, the reaction of **3** (53.3 mg, 0.43 mmol) with aryl imine **78f** (119.3 mg, 0.43 mmol) and DMAP (7.8 mg, 0.0645 mmol) gave a 94:6 mixture of diastereoisomers **90f/*epi*-90f**. After flash column chromatography (eluent Hex:AcOEt 2:1) major diastereoisomer **90f** (less polar fraction) was isolated pure (120.7 mg, 70% yield) and minor diastereoisomer ***epi*-90f** was not observed after flash column chromatography.

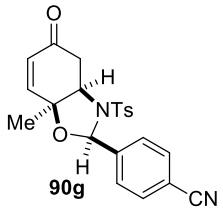
Major diastereoisomer (2*R, 3a*R**, 7a*S**)-90f**:



90f

White solid; **M.p.:** 172-174 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.70 – 7.67 (d, *J* = 8.8 Hz, 2H), 7.41 – 7.33 (m, 4H), 6.99 – 6.91 (m, 2H), 6.16 – 6.12 (dd, *J* = 10.3 and 1.3 Hz, 1H), 6.08 (s, 1H), 5.62 – 5.59 (d, *J* = 10.2 Hz, 1H), 3.90 – 3.87 (m, 1H), 3.33 – 3.25 (ddd, *J* = 17.0, 3.0 and 0.9 Hz, 1H), 2.65 (dd, *J* = 17.1 and 4.6 Hz, 1H), 2.44 (s, 3H), 1.28 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.8, 164.3 - 161.0 (d, *J* = 249 Hz), 148.6, 144.8, 134.7 - 134.7 (d, *J* = 3.2 Hz), 132.5, 129.9 (2C), 128.9 - 128.9 (d, *J* = 8.7 Hz, 2C), 128.6, 128.0 (2C), 115.0 - 114.7 (d, *J* = 21.6 Hz, 2C), 90.3, 79.0, 63.7, 39.7, 23.2, 21.5; **^{19}F NMR (282.4 MHz, $CDCl_3$):** δ = -113.34; **MS (EI) *m/z* (%):** 400 (0.1) [M^+-H], 65 (34), 155 (81), 91 (100); **HRMS Calcd for** $C_{21}H_{19}NO_4FS$ 400.1019, found 400.1011 [M^+-H].

Bicyclic N,O-Acetal 90g.

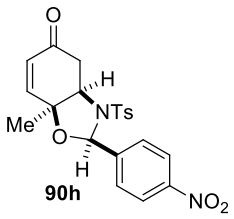


90g

Following general procedure **F**, the reaction of **3** (26 mg, 0.21 mmol) with aryl imine **78g** (59 mg, 0.21 mmol) and DMAP (3.8 mg, 0.031 mmol) gave compound **90g**, as the unique diastereoisomer. Purification by flash column chromatography (eluent Hex:AcOEt 2:1) gave 66 mg of **90g** (77% yield).

White solid; **M.p.:** 204-206 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.74 – 7.71 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 4H), 7.40 – 7.38 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 1H), 6.09 – 6.06 (d, *J* = 10.3 Hz, 1H), 5.58 – 5.55 (d, *J* = 10.3 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.35 – 3.28 (dd, *J* = 17.1 and 3.4 Hz, 1H), 2.68 – 2.60 (dd, *J* = 17.2 and 4.5 Hz, 1H), 2.48 (s, 3H), 1.32 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.3, 148.2, 145.2, 144.3, 132.2, 131.9 (2C), 130.9 (2C), 129.2, 128.2 (2C), 127.8 (2C), 118.4, 112.4, 89.9, 79.7, 63.9, 39.5, 23.2, 21.6; **MS (ESI) *m/z* (%):** 409 (33) [M^++H], 431 (33) [M^++Na], 278 (100); **HRMS Calcd for** $C_{22}H_{21}N_2O_4S$ 409.1216, found 409.1222 [M^++H].

Bicyclic N,O-Acetal 90h.



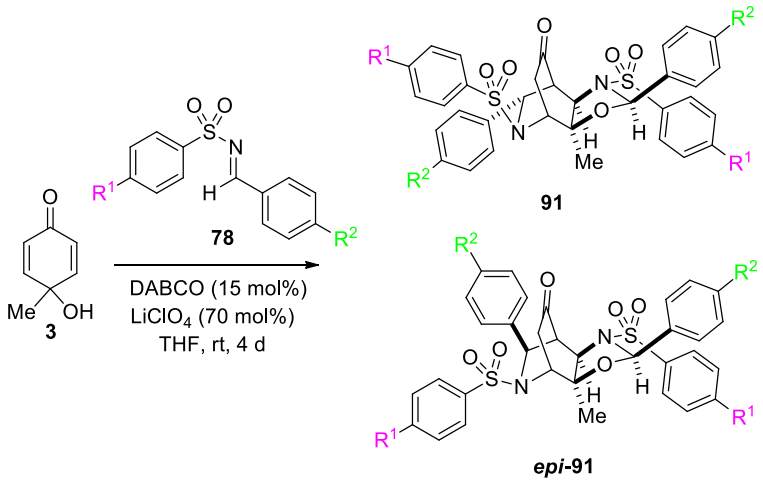
90h

Following general procedure **F**, the reaction of **3** (16 mg, 0.21 mmol) with aryl imine **78h** (40 mg, 0.21 mmol) and DMAP (2.3 mg, 0.02 mmol) gave compound **90h**, as the unique diastereoisomer. Purification by flash column chromatography (eluent Hex:AcOEt 2:1) gave 39 mg of **90h** (68% yield).

White solid; **M.p.:** 229-231 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.17 – 8.14 (d, *J* = 8.8 Hz, 2H), 7.76 – 7.73 (d, *J* = 8.2 Hz, 2H), 7.65 – 7.62 (d, *J* = 8.7 Hz, 2H), 7.42 – 7.39 (d, *J* = 8.0 Hz, 2H), 6.16 (s, 1H), 6.11 – 6.07 (dd, *J* = 10.4 and 1.3 Hz, 1H), 5.60 – 5.56 (d, *J* = 10.4 Hz, 1H), 3.91 – 3.88 (m, 1H), 3.38 – 3.31 (dd, *J* = 17.1 and 3.4 Hz, 1H), 2.69 – 2.62 (dd, *J* = 17.2 and 4.5 Hz, 1H), 2.49 (s, 3H), 1.34 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.2, 148.2, 147.9, 146.1, 145.3, 132.2, 130.2 (2C), 129.4, 128.3 (2C), 128.1 (2C), 123.3 (2C), 89.9, 79.8, 64.1, 39.5, 23.2, 21.7; **MS (ESI) *m/z* (%):** 429 (33) [M^++H], 446 (39) [M^++NH_4], 451 (59) [M^++Na], 278 (100); **HRMS Calcd for** $C_{21}H_{21}N_2O_6S$ 429.1114, found 429.1122 [M^++H].

General procedure for the synthesis of tricyclic derivatives 91

GENERAL PROCEDURE G

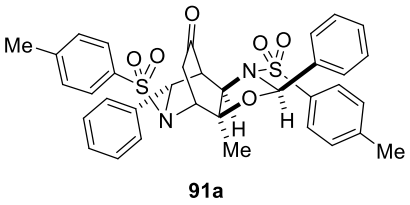


To a mixture of *p*-quinol derivative **3** (1 equiv), the corresponding arylsulfonyl aryl aldimine **78** (2 equiv), $LiClO_4$ (70 mol%) and DABCO (15 mol%) was added THF (0.5 M) under argon. The mixture was stirred at room temperature during 4 days. The crude mixture was concentrated in vacuo and purified by flash column chromatography (eluent indicated in each case).

Tricyclic Derivatives 91a-f.

Tricyclic 91a.

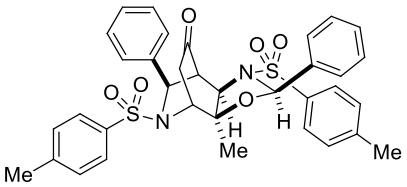
Following general procedure **G**, the reaction of **3** (30 mg, 0.24 mmol) with aryl imine **78a** (120.5 mg, 0.48 mmol), DABCO (4 mg, 0.036 mmol) and $LiClO_4$ (18 mg, 0.17 mmol) gave **91a**, as the unique diastereoisomer. Purification by flash column chromatography (eluent Hex:AcOEt 3:1) gave 77 mg of **91a** (50% yield).



White solid; **M.p.:** Decomposes > 250°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.80 – 7.88 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.41 (m, 8H), 7.41 – 7.38 (m, 8H), 5.68 (s, 1H), 5.12 – 5.12 (d, *J* = 1.4 Hz, 1H), 4.45 – 4.43 (t, *J* = 2.7 Hz, 1H), 3.98 – 3.97 (d, *J* = 2.9 Hz, 1H), 3.19 – 3.17 (dd, *J* = 2.9 and 1.9 Hz, 1H), 2.80 – 2.83 (dd, *J* = 19.4 and 2.6 Hz, 1H), 2.58 (s, 3H), 2.55 (s, 3H), 2.08 – 2.02 (dd, *J* = 19.5 and 2.9 Hz, 1H), 1.53 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 207.3, 144.7, 144.3, 137.3, 135.5, 134.5, 131.8, 129.9 (2C), 129.5, 129.4 (2C), 128.3 (2C), 128.1 (2C), 127.7 (5C), 127.4 (2C), 126.3

(2C), 91.1, 80.9, 60.9, 58.7, 58.5, 57.4, 37.1, 21.3 (2C), 20.4; **MS (ESI) *m/z* (%):** 660 (24) [M^++NH_4], 643 (25) [M^++H], 665 (76) [M^++Na], 537 (100); **HRMS Calcd for** $C_{35}H_{34}N_2O_6NaS_2$ 665.1750, found 665.1757 [M^++Na].

Tricyclic *epi*-91a.



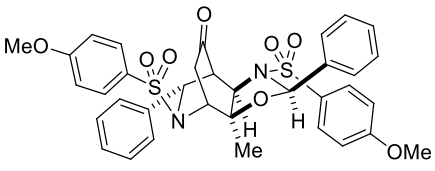
***epi*-91a**

To a mixture of *p*-quinol **3** (41.6 mg, 0.33 mmol) with aryl imine **78a** (168 mg, 0.48 mmol) in MeOH (0.66 ml) was added Cs_2CO_3 (16.4 mg, 0.05 mmol). The mixture was stirred at room temperature during 3 days. The crude mixture was concentrated in vacuo and gave a 60:40 mixture of diastereoisomers **91a**/***epi*-91a** separated after flash column chromatography (eluent Hex:AcOEt 3:1): major diastereoisomer **91a** (less polar fraction) 63 mg, 30% yield and minor diastereoisomer ***epi*-91a** (most polar fraction) 21.7 mg, 10% yield

White solid; **M.p.:** Decomposes > 250°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.30 – 6.92 (m, 16H), 6.79 – 6.76 (d, *J* = 8.1 Hz, 2H), 5.69 (s, 1H), 5.06 – 5.05 (d, *J* = 2.1 Hz, 1H), 4.75 – 4.73 (t, *J* = 2.9 Hz, 1H), 4.33 – 4.32 (d, *J* = 3.4 Hz, 1H), 3.30 – 3.28 (dd, *J* = 3.4 and 2.0 Hz, 1H), 3.20 – 3.13 (dd, *J* = 19.3 and 2.6 Hz, 1H), 2.62 – 2.54 (dd, *J* = 19.3 and 3.4 Hz, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 1.80 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 206.6, 143.9, 142.9, 138.8, 135.9, 134.4, 133.8, 129.7, 129.0 (2C), 128.9 (2C), 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.9 (2C), 127.9, 127.4 (2C), 126.5 (2C), 90.8, 81.2, 66.3, 60.1, 57.6 (2C), 42.2, 23.4, 21.4, 21.3; **MS (ESI) *m/z* (%):** 660 (12) [M^++NH_4], 665 (23) [M^++Na], 643 (45) [M^++H], 537 (100); **HRMS Calcd for** $C_{35}H_{34}N_2O_6NaS_2$ 665.1750, found 665.1728 [M^++Na].

Tricyclic 91b.

Following general procedure **G**, the reaction of **3** (197 mg, 1.6 mmol) with aryl imine **78b** (876 mg, 3.18 mmol), DABCO (27 mg, 0.24 mmol) and $LiClO_4$ (118.7 mg, 1.12 mmol) gave **91b**, as the unique diastereoisomer. Purification by flash column chromatography (eluent Hex:AcOEt 3:1) gave 863 mg of **91b** (80% yield).

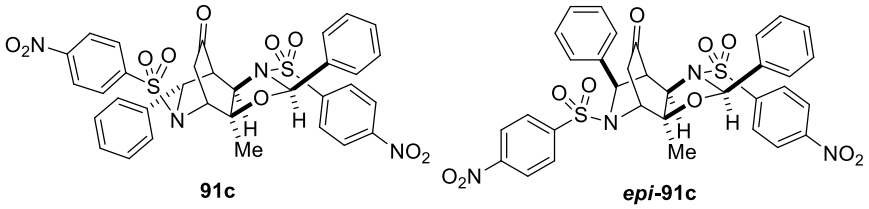


91b

Pale yellow solid; **M.p.:** Decomposes > 250°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.70 – 7.67 (d, *J* = 8.9 Hz, 2H), 7.45 – 7.23 (m, 10H), 7.18 – 7.15 (d, *J* = 8.9 Hz, 2H), 6.97 – 6.94 (d, *J* = 8.9 Hz, 2H), 6.77 – 6.74 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 1H), 4.98 (s, 1H), 4.30 – 4.28 (t, *J* = 2.7 Hz, 1H), 3.87 (s,

3H), 3.85 (s, 3H), 3.03 – 3.01 (t, *J* = 2.4 Hz, 1H), 2.69 – 2.62 (dd, *J* = 19.4 and 2.5 Hz, 1H), 2.02 - 1.95 (dd, *J* = 19.6 and 3.0 Hz, 1H), 1.43 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 207.4, 163.4, 163.1, 137.4, 135.5, 129.9 (2C), 129.5 (3C), 128.9, 128.3 (2C), 128.1 (2C), 127.7 (2C), 127.6, 126.3, 126.2 (2C), 114.4, 113.9, 91.1, 80.8, 60.9, 58.6, 58.3, 57.4, 55.4, 55.4, 37.2, 20.4; **MS (FAB) *m/z* (%):** 675 (3) [M^++H], 663 (45), 57 (85), 73 (100); **HRMS Calcd for** $C_{35}H_{35}N_2O_8S_2$ 675.1835, found 675.1830 [M^++H].

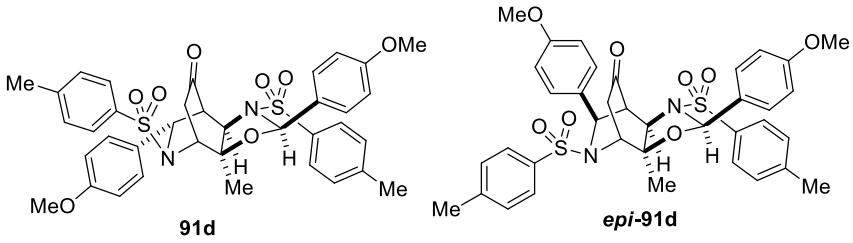
Tricyclic 91c/*epi*-91c.



Following general procedure **G**, the reaction of **3** (50 mg, 0.40 mmol) with aryl imine **78c** (234 mg, 0.80 mmol), DABCO (6.8 mg, 0.06 mmol) and $LiClO_4$ (30 mg, 0.28 mmol) gave a 75:25 mixture of diastereoisomers **91c/*epi*-91c**. After flash column chromatography (eluent Hex:AcOEt 3:1) a fraction containing a 40:60 mixture of **91c/*epi*-91c** could be isolated (116 mg, 48% yield).

^{1}H NMR (300 MHz, $CDCl_3$) of a 40:60 mixture of **91c/*epi*-91c**: δ = 8.30 – 8.27(d, *J* = 8.7 Hz, 1.3H, (**91c**)), 8.00 – 7.97 (d, *J* = 8.6 Hz, 1.3H, (**91c**)), 7.99 – 7.96 (d, *J* = 8.8 Hz, 2H, (***epi*-91c**)), 7.92 – 7.89 (d, *J* = 8.8 Hz, 2H, (***epi*-91c**)),7.86 – 7.83 (d, *J* = 8.8 Hz, 1.3H, (**91c**)) 7.42 – 7.02 (m, 12H (***epi*-91c**) + 7.8H (**91c**)), 6.82 – 6.80 (d, *J* = 7.7 Hz, 2H, (***epi*-91c**)), 5.81 (s, 1H, (***epi*-91c**)), 5.67 (s, 0.65H, (**91c**)), 5.22 – 5.21 (d, *J* = 1.7 Hz, 0.65H, (**91c**)), 5.10 – 5.09 (d, *J* = 2.0 Hz, 1H, (***epi*-91c**)), 4.85 – 4.83 (t, *J* = 2.8 Hz, 1H, (***epi*-91c**)), 4.61 – 4.59 (t, *J* = 2.7 Hz, 0.65H, (**91c**)), 4.54 – 4.53 (d, *J* = 3.5 Hz, 1H, (***epi*-91c**)), 4.26 – 4.25 (d, *J* = 3.0 Hz, 0.65H, (**91c**)), 3.38 – 3.37 (dd, *J* = 3.4 and 1.9 Hz, 1H, (***epi*-91c**)), 3.30 – 3.23 (dd, *J* = 19.7 and 2.5 Hz, 1H, (***epi*-91c**)), 3.19 – 3.18 (t, *J* = 2.2 Hz, 0.65H, (**91c**)), 2.99 – 2.92 (dd, *J* = 19.5 and 2.6 Hz, 0.65H, (**91c**)), 2.70 – 2.62 (dd, *J* = 19.5 and 3.3 Hz, 1H, (***epi*-91c**)), 2.49 – 2.41 (dd, *J* = 19.5 and 2.7 Hz, 0.65H, (**91c**)), 1.97 (s, 3H, (***epi*-91c**)), 1.71 (s, 1.95H, (**91c**)); **^{13}C NMR (75 MHz, $CDCl_3$)** of a 40:60 mixture of **91c/*epi*-91c:** δ = 206.8, 206.2, 150.5, 149.8, 149.7, 149.5, 147.0, 144.2, 143.9, 143.2, 135.6, 135.2, 132.8, 132.3, 130.5, 130.5, 129.1, 129.1, 129.05, 129.02, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.4, 127.8, 127.7, 126.6, 124.4, 123.6, 123.5, 123.2, 90.6, 81.3, 80.8, 65.9, 60.8, 60.0, 59.8, 58.9, 58.0, 57.1, 56.8, 42.2, 38.9, 30.9, 29.7, 23.5, 21.5; **MS (ESI) *m/z* (%):** 727 (100) [M^++Na], 172 (36), 728 (16); **HRMS Calcd for** $C_{33}H_{28}N_4O_{10}NaS_2$ 727.1139, found 727.1139 [M^++Na].

Tricyclic 91d/*epi*-91d.



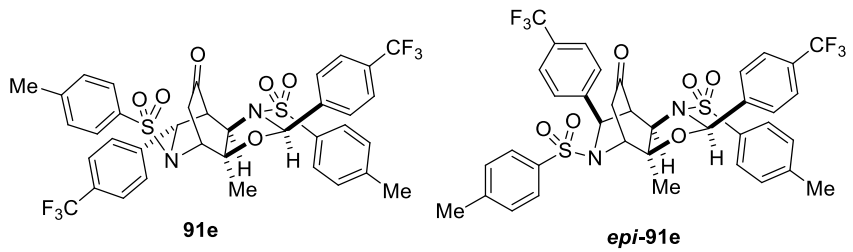
91d ***epi*-91d**

Following general procedure **G**, the reaction of **3** (108 mg, 0.87 mmol) with aryl imine **78d** (504 mg, 1.74 mmol), DABCO (14.6 mg, 0.13 mmol) and $LiClO_4$ (64.6 mg, 0.61 mmol) gave a 92:8 mixture of diastereoisomers **91d/*epi*-91d**. After flash column chromatography (eluent Hex:AcOEt 3:1) major diastereoisomer **91d** (less polar fraction) was isolated pure (250 mg, 41% yield) whereas minor diastereoisomer ***epi*-91d** was not observed after flash column chromatography.

Major diastereoisomer 91d:

Yellow solid; **M.p.:** Decomposes > 250°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.62 – 7.59 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.26 (d, *J* = 9.0 Hz, 2H), 7.24 – 7.23 (d, *J* = 4.2 Hz, 2H), 7.16 – 7.08 (m, 6H), 6.96 – 6.93 (d, *J* = 8.7 Hz, 2H), 6.75 – 6.72 (d, *J* = 8.6 Hz, 2H), 5.48 (s, 1H), 4.90 (s, 1H), 4.28 – 4.27 (t, *J* = 2.7 Hz, 1H), 3.86 (s, 3H), 3.85 – 3.84 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 2.99 – 2.98 (t, *J* = 2.4 Hz, 1H), 2.65 – 2.57 (dd, *J* = 19.4 and 2.6 Hz, 1H), 2.41 (s, 3H), 2.37 (s, 3H), 1.93 – 1.86 (dd, *J* = 19.4 and 2.8 Hz, 1H), 1.37 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 207.8, 160.5, 159.0, 144.6, 144.1, 134.8, 132.4, 129.9 (2C), 129.3 (2C), 129.2 (2C), 129.1, 127.9 (2C), 127.5 (2C), 127.4 (2C), 127.3, 113.8 (2C), 113.6 (2C), 90.8, 80.6, 60.9, 58.9, 58.1, 57.7, 55.2, 55.0, 37.2, 21.4 (2C), 20.6; **MS (FAB) *m/z* (%):** 703 (19) [M^++H], 702 (20) [M^+], 136 (86), 154 (100); **HRMS Calcd for** $C_{37}H_{39}N_2O_8S_2$ 703.2148, found 703.2148 [M^++H].

Tricyclic 91e/*epi*-91e.



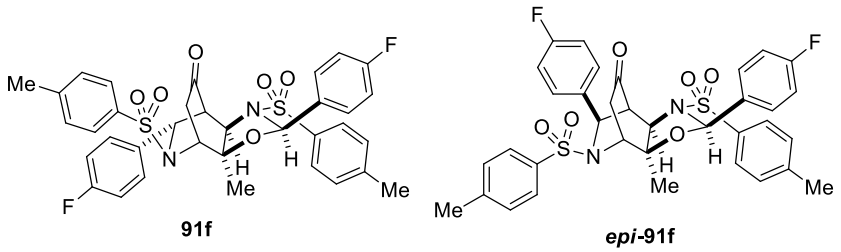
91e ***epi*-91e**

Following general procedure **G**, the reaction of **3** (70 mg, 0.53 mmol) with aryl imine **78e** (367 mg, 1.12 mmol), DABCO (9.4 mg, 0.08 mmol) and $LiClO_4$ (41.7 mg, 0.39 mmol) gave a 85:15 mixture of diastereoisomers **91e/*epi*-91e**. After flash column chromatography (eluent Hex:AcOEt 3:1) major diastereoisomer **91e** (less polar fraction) was isolated pure (205 mg, 47% yield) whereas minor diastereoisomer ***epi*-91e** was not observed after flash column chromatography.

Major diastereoisomer 91e:

Pink solid; **M.p.:** Decomposes > 250°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.73 – 7.71 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.63 (d, *J* = 8.3 Hz, 2H), 7.52 – 7.49 (d, *J* = 8.2 Hz, 2H), 7.49 – 7.47 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.31 (d, *J* = 8.1 Hz, 4H), 7.08 (s, 4H), 5.62 (s, 1H), 5.01 (s, 1H), 4.34 – 4.32 (t, *J* = 2.7 Hz, 1H), 3.76 – 3.75 (d, *J* = 2.9 Hz, 1H), 3.06 – 3.04 (m, 1H), 2.62 – 2.55 (dd, *J* = 19.5 and 2.6 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H), 1.96 – 1.88 (dd, *J* = 19.5 and 2.9 Hz, 1H), 1.46 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 206.8, 145.4, 144.9, 141.6, 138.9, 134.5, 132.5, 130.4 (2C), 129.6 (2C), 128.5 (2C), 128.0 (2C), 127.8 (2C), 127.0 (2C), 125.7 (q, *J* = 4.6Hz, 2C) 125.3 (q, *J* = 4.6Hz, 2C), 90.4, 81.6, 61.2, 58.9, 58.3, 57.1, 37.4, 21.6, 21.5, 20.9; **^{19}F NMR (282.4 MHz, $CDCl_3$):** δ = -62.52, -62.92; **MS (ESI) *m/z* (%):** 801 (19) [M^++Na], 779 (20) [M^++H], 265 (74), 301 (100); **HRMS Calcd for** $C_{37}H_{32}N_2O_6F_6NaS_2$ 801.1498, found 801.1482 [M^++Na].

Tricyclic 91f/*epi*-91f.

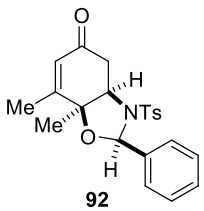


Following general procedure **G**, the reaction of **3** (44 mg, 0.35 mmol) with aryl imine **78f** (196 mg, 0.706 mmol), DABCO (6 mg, 0.05 mmol) and $LiClO_4$ (26.3 mg, 0.24 mmol) gave a 90:10 mixture of diastereoisomers **91f/*epi*-91f**. After flash column chromatography (eluent Hex:AcOEt 3:1) major diastereoisomer **91f** (less polar fraction) was isolated pure (95 mg, 40% yield) whereas minor diastereoisomer ***epi*-91f** was not observed after flash column chromatography.

Major diastereoisomer 91f:

Pink solid; **M.p.:** Decomposes > 250°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.64 – 7.62 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.30 (m, 4H), 7.22 – 7.11 (m, 8H), 6.94 – 6.89 (t, *J* = 8.7 Hz, 2H), 5.54 (s, 1H), 4.94 (s, 1H), 4.31 – 4.29 (t, *J* = 2.7 Hz, 1H), 3.82 – 3.81 (d, *J* = 2.9 Hz, 1H), 3.00 – 2.98 (dd, *J* = 2.9 and 1.9 Hz, 1H), 2.63 – 2.55 (dd, *J* = 19.4 and 2.6 Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H), 1.93 – 1.86 (dd, *J* = 19.5 and 2.8 Hz, 1H), 1.41 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 207.4, 165.2 – 161.9 (d, *J* = 249 Hz), 163.9 – 160.6 (d, *J* = 245 Hz), 145.1, 144.7, 134.7, 133.2 – 133.1 (d, *J* = 3.3 Hz), 132.7, 131.2 - 131.1 (d, *J* = 3.1 Hz), 130.3 (2C), 130.0 - 129.9 (d, *J* = 8.6 Hz, 2C), 129.5 (2C), 128.3 - 128.2 (d, *J* = 8.1 Hz, 2C), 128.0 (2C), 127.7 (2C), 115.7 - 115.5 (d, *J* = 16.3 Hz, 2C), 115.4 - 115.2 (d, *J* = 16.3 Hz, 2C), 90.5, 81.1, 61.1, 59.0, 58.2, 57.6, 37.3, 21.6, 21.6, 20.9; **^{19}F NMR (282.4 MHz, $CDCl_3$):** δ = -111.11, -113.85; **MS (ESI) *m/z* (%):** 696 (17) [M^++NH_4], 679 (37) [M^++H], 701 (40) [M^++Na], 149 (86), 555 (100); **HRMS Calcd for** $C_{35}H_{33}N_2O_6F_2S_2$ 679.1742, found 679.1741 [M^++H].

Bicyclic N,O-Acetal 92.



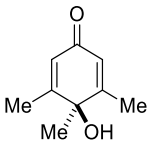
92

Following general procedure **G**, the reaction of **777** (60 mg, 0.43 mmol) with aryl imine **78a** (218 mg, 0.87 mmol), DABCO (7.3 mg, 0.065 mmol) and $LiClO_4$ (32.3 mg, 0.30 mmol) gave **92**, as the unique diastereoisomer. Purification by flash column chromatography (eluent Hex:AcOEt 2:1) gave 147 mg of **92** (86% yield).

White solid; **M.p.:** 189-192°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.69 - 7.66 (d, *J* = 8.1 Hz, 2H), 7.35 – 7.26 (m, 7H), 6.13 (s, 1H), 5.61 (s, 1H), 3.93 – 3.90 (t, *J* = 4.1 Hz, 1H), 3.43 – 3.36 (dd, *J* = 17.1 and 3.7 Hz, 1H), 2.68 – 2.61 (dd, *J* = 17.1 and 4.6 Hz, 1H), 2.45 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 194.4, 159.0, 144.6, 137.8, 132.8, 129.9 (2C), 128.6, 128.2, 128.1 (2C), 127.8 (2C), 127.3 (2C), 91.2, 81.1, 64.6, 39.1, 22.2, 21.6, 18.2; **MS (FAB) *m/z* (%):** 398 (11) [M^++H], 260 (55), 172 (59), 137 (100); **HRMS Calcd for** $C_{22}H_{24}NO_4S$ 398.1426, found 398.1441 [M^++H].

EXPERIMENTAL PART OF CHAPTER 3.1: Intermolecular FC reactions of different heteroaromatic derivatives with *p*-quinols.

4-Hydroxy-3,4,5-trimethyl-2,5-cyclohexadien-1-one 170.

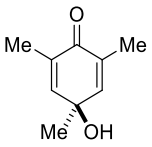


170

Following the general procedure **A**, *p*-alkylphenol **169** (1.1 g, 8.2 mmol) was dissolved in a 1.6:1 mixture of H_2O (154 ml)/CH_3CN (96 ml). Then, Oxone® (40 g, 65.6 mmol) and $NaHCO_3$ (16.6 g, 197 mmol) were added and the reaction was stirred at room temperature until the consumption of the starting material. Then, the crude reaction was diluted with 100 ml of H_2O and $Na_2S_2O_3$ (13 g, 82 mmol) were added. After 30 min, the reaction was quenched with water and extracted with AcOEt affording 1 g (83% yield) of **170** which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$):[36] δ = 5.73 (s, 2H), 4.36 (brs, 1H), 1.95 (s, 6H), 1.28 (s, 3H).

4-Hydroxy-2,4,6-trimethyl-2,5-cyclohexadien-1-one 172.

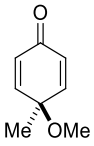


172

Following the general procedure **A**, *p*-alkylphenol **171** (2 g, 14.7 mmol) was dissolved in a 4:1 mixture of H_2O (200 ml)/CH_3CN (50 ml). Then, Oxone® (72 g, 117.6 mmol) and $NaHCO_3$ (29 g, 352.3 mmol) were added and the reaction was stirred at room temperature until the consumption of the starting material. Then, the crude reaction was diluted with 150 ml of H_2O and $Na_2S_2O_3$ (23 g, 147 mmol) were added. After 30 min, the reaction was quenched with water and extracted with AcOEt affording 2.1 g (95% yield) of **172** which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$):[36] δ = 6.58 (s, 2H), 2.97 (brs, 1H), 1.79 (s, 6H), 1.37 (s, 3H).

4-methyl-4-methoxy-cyclohexa-2,5-dienone 97.



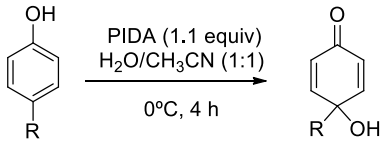
97

p-Cresol **1** (1 g, 9.24 mmol) was dissolved in 30 ml of MeOH at 0°C. Then, PIDA (3.27 g, 10.16 mmol) was added and the reaction was stirred at room temperature until the consumption of the starting material. After removing the solvent in vacuo, water is added and the crude mixture is extracted with AcOEt affording after purification by flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 1 g (80% yield) of **97**.

^{1}H NMR (300 MHz, $CDCl_3$):[122] δ = 6.79 – 6.75 (d, *J* = 10.1 Hz, 2H), 6.33 – 6.30 (d, *J* = 10.1 Hz, 2H), 3.21 (s, 3H), 1.43 (s, 3H).

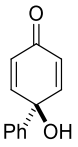
General procedure for the synthesis of *p*-quinols using Hypervalent iodo reagents

GENERAL PROCEDURE H.[123]



The phenol (1 equiv) is dissolved in a 50/50 mixture of CH_3CN/H_2O (0.1 M), and the resulting solution is stirred vigorously at 0°C as PIDA (1.2 equiv) is added. When the starting material is consumed the crude reaction is extracted with EtOAc. The combined EtOAc extracts are dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under vacuum. *p*-quinol is obtained from the crude after purification, explained in each case.

4-Hydroxy-4-phenyl-2,5-cyclohexadienone 174.

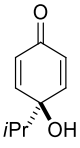


174

Following the general procedure **H**, *p*-alkylphenol **173** (1.04 g, 6.09 mmol) was dissolved in a 1:1 mixture of H_2O (30 ml)/CH_3CN (30 ml). Then, PIDA (2.35 g, 7.3 mmol) was added and the reaction was stirred at room temperature until the consumption of the starting material. Then, the crude reaction was quenched with water and extracted with AcOEt affording after recristallization from hexanes 487 mg (43% yield) of **174**.

^{1}H NMR (300 MHz, $CDCl_3$):[123] δ = 7.54 – 7.44 (m, 2H), 7.43 – 7.30 (m, 3H), 6.92 – 6.88 (d, *J* = 10.0 Hz, 2H), 6.25 – 6.22 (d, *J* = 10.0 Hz, 2H).

4-hydroxy-4-isopropylcyclohexa-2,5-dienone 37.

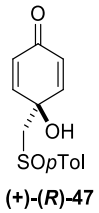


37

Following the general procedure **H**, *p*-alkylphenol **175** (526 mg, 3.86 mmol) was dissolved in a 1:1 mixture of H_2O (19 ml)/CH_3CN (19 ml). Then, PIDA (1.49 g, 4.6 mmol) was added and the reaction was stirred at room temperature until the consumption of the starting material. Then, the crude reaction was quenched with water and extracted with AcOEt affording after purification by flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 428 mg (73% yield) of **37**.

^{1}H NMR (300 MHz, $CDCl_3$):[124] δ = 6.82 – 6.78 (d, *J* = 10.2 Hz, 2H), 6.17 – 6.13 (d, *J* = 10.2 Hz, 2H), 2.03 – 1.92 (m, 1H), 0.93 – 0.91 (d, *J* = 6.9 Hz, 6H).

***p*-Tolylsulfinylmethyl-cyclohexa-2,5-dienone (+)-(*R*)-47.**[48]



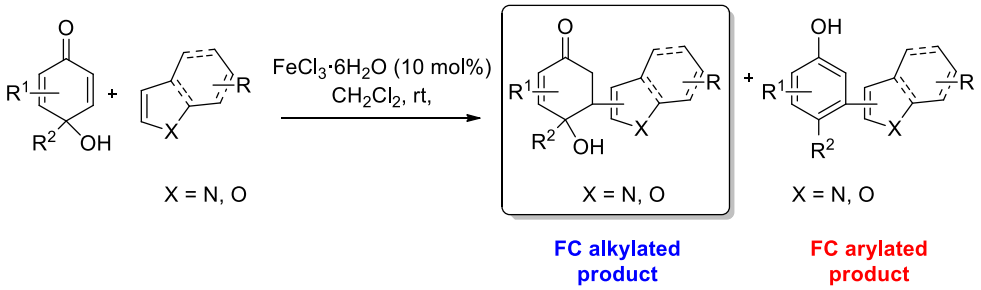
(+)-(*R*)-47

The addition of an anhydrous THF solution of *p*-benzoquinone dimethyl monoketal **44** (1.05 equiv) to (*R*)-methyl-*p*-tolylsulfoxide **45** (1 equiv) and LDA (1.1 eq) in THF at -78°C afforded the intermediate ketal derivative **46** that was treated with a 5 mol% solution of oxalic acid in a 4:1 mixture of THF/H_2O to obtain the *p*-quinol **47** with an overall yield of 80%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 - 7.52 (AA', 2H), 7.38 - 7.34 (BB', 2H), 7.25 (dd, *J* = 10.2 and 3.2 Hz, 1H), 7.00 (dd, *J* = 10.2 and 3.2 Hz, 1H), 6.29 (dd, *J* = 10.2 and 1.8 Hz, 1H), 6.18 (dd, *J* = 10.1 and 1.9 Hz, 1H), 4.93 (brs, 1H), 3.16 and 2.85 (AB, *J* = 13.3 Hz, 2H), 2.43 (s, 3H).

General procedure for racemic FC reaction of indoles, pyrrols and furans with *p*-quinols.

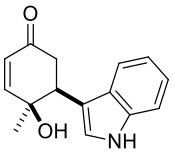
GENERAL PROCEDURE I



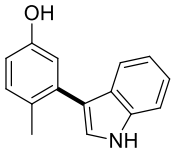
A mixture of the corresponding *p*-quinol (1 equiv) and the indicated indole, pyrrol or furan (1.1 equiv) was dissolved in CH_2Cl_2 (0.1 M) at room temperature. $FeCl_3·6H_2O$ (10 mol%) was then added and the mixture was stirring until the starting material was judged disappeared by TLC. Then, the crude mixture was filtered through a pad of celite and the resulting organic phase was washed with water and dried over anhydrous $MgSO_4$. The solvent was then removed under reduced pressure. The crude product was purified by flash chromatography using the eluent indicated in each case.

FC reaction of indoles to *p*-quinols

(4*S*,5*S*)-4-hydroxy-5-(1H-indol-3-yl)-4-methylcyclohex-2-enone 177a and 3-(1H-indol-3-yl)-4-methylphenol 178a.



177a



178a

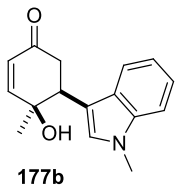
Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), 1*H*-indole **176a** (104.2 mg, 0.887 mmol) and $FeCl_3·6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8

ml) gave a 92:8 mixture of **177a/178a**. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 9 mg (5% yield) of **178a** (less polar fraction) were obtained as a brown oil and 175 mg (90% yield) of **177a** (most polar fraction) were obtained pure as a dark green solid. Reaction time: 2 h.

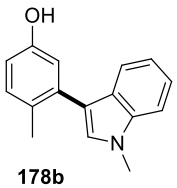
Signals for **177a: M.p.:** 147-149 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.42 (brs, 1H), 7.64- 7.61 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.36 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.13 (m, 2H), 7.08 – 7.07 (d, *J* = 2.5 Hz, 1H), 6.84 – 6.80 (d, *J* = 10.1 Hz, 1H), 6.08 – 6.06 (d, *J* = 10.1 Hz, 1H), 3.71 – 3.66 (dd, *J* = 10.6 and 4.2 Hz, 1H), 3.11 – 3.02 (dd, *J* = 16.6 and 10.6 Hz, 1H), 2.70 – 2.63 (dd, *J* = 16.6 and 4.3 Hz, 1H), 1.44 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 199.9, 153.5, 135.9, 128.5, 127.6, 122.8, 122.5, 119.9, 119.2, 114.1, 111.3, 69.5, 41.9, 41.1, 28.1; **MS (EI) *m/z* (%):** 241 (12) [M^+], 222 (48), 223 (61), 143 (100); **HRMS Calcd for** $C_{15}H_{15}NO_2$ 241.1103, found 241.1109 [M^+].

Signals for **178a**:[26] **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.22 (brs, 1H), 7.56 – 7.54 (d, *J* = 7.9 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.25 – 7.12 (m, 4H), 6.93 – 6.92 (d, *J* = 2.8 Hz, 1H), 6.78 – 6.74 (dd, *J* = 8.2 and 2.8 Hz, 1H), 4.61 (bs, 1H), 2.24 (s, 3H).

(4S,5S)-4-hydroxy-4-methyl-5-(1-methyl-1H-indol-3-yl)cyclohex-2-enone 177b and 4-methyl-3-(1-methyl-1H-indol-3-yl)phenol 178b



177b



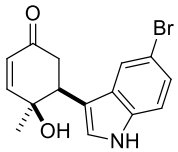
178b

Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), 1-methyl-indole **176b** (110.7 µl, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8 ml) gave a 75:25 mixture of **177b/178b**. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 50.7mg (24% yield) of **178b** (less polar fraction) were obtained as a dark brown oil and 133.7 mg (64% yield) of **177b** (most polar fraction) were obtained pure as a brown oil. Reaction time: 40 min.

Signals for **177b**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.55 – 7.51 (dq, *J* = 8.0 and 1.1 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.10 – 7.04 (m, 1H), 6.89 (s, 1H), 6.76 – 6.72 (dd, *J* = 10.1 and 1.0 Hz, 1H), 6.00 – 5.97 (d, *J* = 10.0 Hz, 1H), 3.71 (s, 3H), 3.64 – 3.59 (dd, *J* = 10.3 and 4.4 Hz, 1H), 3.01 – 2.92 (ddd, *J* = 16.6, 10.2 and 1.0 Hz, 1H), 2.63 – 2.56 (dd, *J* = 16.6 and 4.4 Hz, 1H), 1.38 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 199.8, 153.5, 136.6, 128.4, 128.1, 127.3, 121.9, 119.4, 119.2, 112.5, 109.3, 69.4, 41.8, 41.2, 32.7, 28.0; **MS (ESI) *m/z* (%):** 278 (12) [M^++Na], 273 (17) [M^++NH_4], 238 (44), 256 (100) [M^++H]; **HRMS Calcd for** $C_{16}H_{18}NO_2$ 256.1332, found 256.1327 [M^++H].

Signals for **178b**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.56 – 7.53 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.36 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.17 – 7.10 (m, 2H), 7.00 (s, 1H), 6.90 – 6.89 (d, *J* = 2.8 Hz, 1H), 6.74 – 6.71 (dd, *J* = 8.2 and 2.9 Hz, 1H), 3.81 (s, 3H), 2.25 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 153.3, 136.6, 135. 7, 131.3, 128.6, 127.5, 127.3, 121.7, 120.2, 119.4, 117.4, 115.6, 113.4, 109.3, 32.7, 19.8; **MS (EI) *m/z* (%):** 222 (21), 236 (84), 237 (100) [M^+]; **HRMS Calcd for** $C_{16}H_{15}NO$ 237.1154, found 237.1157 [M^+].

(4*S*,5*S*)-5-(5-bromo-1H-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 177d.

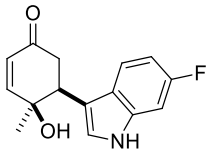


177d

Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), 5-bromo-1*H*-indole **176d** (173.9 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8 ml) gave **177d** as the only product. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 223.6 mg (87% yield) of **177d** were obtained as a brown solid. Reaction time: 2.5 hours.

M.p.: decomposes; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.28 (brs, 1H), 7.68 (s, 1H), 7.25 – 7.17 (m, 2H), 7.07 – 7.06 (d, *J* = 2.5 Hz, 1H), 6.77 – 6.73 (dd, *J* = 10.1 and 0.9 Hz, 1H), 6.01 – 5.98 (d, *J* = 10.1 Hz, 1H), 3.57 – 3.52 (dd, *J* = 10.6 and 4.3 Hz, 1H), 3.02 – 2.92 (ddd, *J* = 16.6, 10.6 and 0.9 Hz, 1H), 2.62 – 2.5 (dd, *J* = 16.6 and 4.3 Hz, 1H), 1.37 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 200.1, 153.7, 134.4, 129.3, 128.4, 125.1, 124.1, 121.7, 113.7, 113.1, 112.8, 69.4, 41.7, 41.0, 27.9**; MS (ESI) *m/z* (%):** 342 (17) [M^++Na], 300 (59), 320 (100) [M^++H]; **HRMS Calcd for** $C_{15}H_{15}NO_2Br$ 320.0280, found 320.0281 [M^++H].

(4*S*,5*S*)-5-(6-fluoro-1H-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 177e.



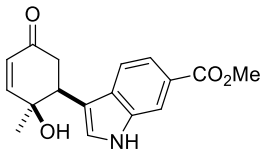
177e

Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), 6-fluoro-1*H*-indole **176e** (119.8 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8 ml) gave **177e** as the only product. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 198.3 mg (95% yield) of **177e** were obtained as a brown oil. Reaction time: 50 min.

^{1}H NMR (300 MHz, $CDCl_3$); δ = 8.68 (brs, 1H), 7.52 – 7.47 (dd, *J* = 8.8 and 5.2 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.92 – 6.86 (td, *J* = 9.2 and 2.3 Hz, 1H), 6.83 – 6.80 (d, *J* = 10.1 Hz, 1H), 6.06 – 6.01 (d, *J* = 10.1 Hz, 1H), 3.64 – 3.59 (dd, *J* = 10.7 and 4.2 Hz, 1H), 3.07 – 2.98 (dd, *J* = 16.7 and 10.7 Hz, 1H), 2.65 – 2.59 (dd, *J* = 16.6 and 4.2 Hz, 1H), 1.41 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 200.1, 161.5 – 158.4 (d, *J* = 238.4 Hz), 153.6, 135.9 - 135.7 (d, *J* = 12.3 Hz), 128.4, 124.2, 123.1 - 123.0 (d, *J* = 3.5 Hz), 119.9 - 119.8 (d, *J* = 10.3 Hz), 114.2, 108.8 - 108.5 (d, *J* = 24.8 Hz), 97.7 -

97.4 (d, *J* = 25.9 Hz), 69.4, 41.8, 41.0, 27.9; **^{19}F NMR (282.4 MHz, $CDCl_3$):** δ = -120.28; **MS (EI) *m/z* (%):** 259 (8) [M^+], 241 (16), 161 (100); **HRMS Calcd for** $C_{15}H_{14}NO_2F$ 259.1009, found 259.1017 [M^+].

Methyl-3-((1S,2S)-2-hydroxy-2-methyl-5-oxocyclohex-3-en-1-yl)-1H-indole-6-carboxylate 177f.

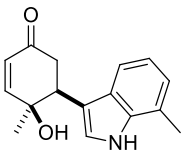


177f

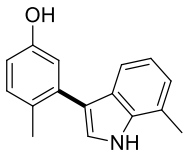
Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), methyl 1*H*-indole-6-carboxylate **176f** (155.4 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8 ml) gave **177f** as the only product. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 198 mg (82%) of **177f** were obtained as a dark brown oil. Reaction time: 2 hours.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (brs, 1H), 8.14 (s, 1H), 7.84 – 7.80 (dd, *J* = 8.5 and 1.3 Hz, 1H), 7.65 – 7.62 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.30 (d, *J* = 2.5 Hz, 1H), 6.85 – 6.81 (dd, *J* = 10.1 and 0.9 Hz, 1H), 6.09 – 6.06 (d, *J* = 10.0 Hz, 1H), 3.93 (s, 3H), 3.72 – 3.67 (dd, *J* = 10.8 and 4.2 Hz, 1H), 3.12 – 3.03 (dd, *J* = 16.6 and 10.8 Hz, 1H), 2.70 – 2.63 (dd, *J* = 16.6 and 4.2 Hz, 1H), 1.44 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 200.2, 168.3, 153.7, 135.1, 131.1, 128.3, 126.7, 123.5, 120.5, 118.7, 114.4, 113.8, 69.4, 52.0, 41.6, 40.9, 27.8; **MS (ESI) m/z (%):** 599 (25) [2M^++H], 300 (100) [M^++H]; **HRMS Calcd for** $C_{17}H_{18}NO_4$ 300.1230, found 300.1229 [M^++H].

(4*S*,5*S*)-4-hydroxy-4-methyl-5-(7-methyl-1H-indol-3-yl)cyclohex-2-enone 177i and 4-methyl-3-(7-methyl-1H-indol-3-yl)phenol 178i.



177i



178i

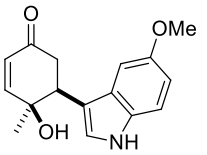
Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), 7-methyl-1*H*-indole **176i** (116.3 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8 ml) gave a 94:6 mixture of **177i/178i**. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 9.5 mg (5% yield) of **178i** (less polar fraction) were obtained as a dark brown oil and 187 mg (91% yield) of **177i** (most polar fraction) were obtained pure as a green solid. Reaction time: 15 hours.

Signals for **177i**: **M.p.:** 159-161°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.39 (brs, 1H), 7.49 – 7.47 (d, *J* = 7.7 Hz, 1H), 7.12 – 7.03 (m, 3H), 6.84 – 6.81 (d, *J* = 10.1 Hz, 1H), 6.08 – 6.05 (d, *J* = 10.1 Hz, 1H), 3.71 – 3.66 (dd, *J* = 10.7 and 4.2 Hz, 1H), 3.12 – 3.03 (dd, *J* = 16.6 and 10.7 Hz, 1H), 2.70 –

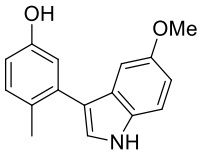
2.63 (dd, *J* = 16.6 and 4.2 Hz, 1H), 2.49 (s, 3H), 1.44 (s, 3H); **^{13}C NMR (75MHz, $CDCl_3$):** δ = 200.0, 153.5, 135.5, 128.5, 127.2, 122.9, 122.5, 120.6, 120.1, 116.9, 114.6, 69.5, 42.0, 41.1, 28.1, 16.5; **MS (EI) *m/z* (%):** 255 (0.6) [M^+], 237 (20), 157 (100); **HRMS Calcd for** $C_{16}H_{17}NO_2$ 255.1259, found 255.1265 [M^+].

Signals for **178i**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.24 (brs, 1H), 7.62 – 7.59 (m, 1H), 7.42 – 7.31 (m, 1H), 7.31 – 7.24 (m, 3H), 7.08 – 7.07 (d, *J* = 2.7 Hz, 1H), 6.96 – 6.93 (dd, *J* = 8.2 and 2.8 Hz, 1H), 5.40 (bs, 1H), 2.70 (s, 3H), 2.43 (s, 3H); **^{13}C NMR (75MHz, $CDCl_3$):** δ = 153.1, 135.7, 135.3, 131.3, 128.9, 126.4, 122.7, 122.6, 120.4, 120.1, 117.8, 117.6, 117.4, 113.6, 19.7, 16.5; **MS (EI) *m/z* (%):** 237 (100) [M^+], 222 (59), 236 (53); **HRMS Calcd for** $C_{16}H_{15}NO$ 237.1154, found 237.1150 [M^+].

(4*S*,5*S*)-4-hydroxy-5-(5-methoxy-1H-indol-3-yl)-4-methylcyclohex-2-enone 177j and 3-(5-methoxy-1H-indol-3-yl)-4-methylphenol 178j.



177j



178j

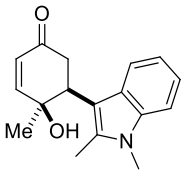
Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), 5-methoxy-1*H*-indole **176j** (130.5 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8 ml) gave a 90:10 mixture of **177j/178j**. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 20 mg (9% yield) of **178j** (less polar fraction) were obtained as a dark brown oil and 153 mg (70% yield) of **177j** (most polar fraction) were obtained pure as a brown oil. Reaction time: 3 days.

Signals for **177j**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.18 (brs, 1H), 7.30 – 7.27 (dd, *J* = 8.9 and 0.7 Hz, 1H), 7.11 – 7.10 (d, *J* = 2.6 Hz, 1H), 7.06 – 7.05 (d, *J* = 2.4 Hz, 1H), 6.91 – 6.88 (dd, *J* = 8.9 and 2.4 Hz, 1H), 6.85 – 6.81 (d, *J* = 10.1 Hz, 1H), 6.09 – 6.06 (dd, *J* = 10.1 and 0.7 Hz, 1H), 3.86 (s, 3H), 3.67 – 3.62 (dd, *J* = 10.5 and 4.3 Hz, 1H), 3.11 – 3.02 (ddd, *J* = 16.6, 10.5 and 0.8 Hz, 1H), 2.72 – 2.64 (ddd, *J* = 16.6, 4.3 and 0.8 Hz, 1H), 1.47 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 200.4, 154.0, 153.8, 131.0, 128.2, 127.9, 123.7, 113.5, 112.3, 112.0, 101.0, 69.4, 55.8, 41.7, 40.9, 27.9; **MS (ESI) *m/z* (%):** 294 (9) [M^++Na], 543 (20) [2M^++H], 254 (80) [M^+-OH], 272 (100) [M^++H]; **HRMS Calcd for** $C_{16}H_{18}NO_3$ 272.1281, found 272.1282 [M^++H].

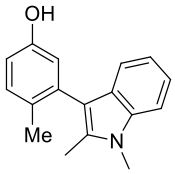
Signals for **178j**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.14 (brs, 1H), 7.33 – 7.30 (d, *J* = 8.7 Hz, 1H), 7.20 – 7.18 (d, *J* = 8.2 Hz, 1H), 7.15 – 7.14 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.78 – 6.75 (dd, *J* = 8.2 and 2.8 Hz, 1H), 4.81 (bs, 1H), 3.81 (s, 3H), 2.24 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 154.4, 153.3, 135.7, 131.3, 131.0, 129.0, 127.4, 123.5, 117.4, 117.1,

113.6, 112.6, 111.9, 101.7, 56.0, 19.7; **MS (EI) *m/z* (%):** 253 (100) [M^+], 238 (80), 210 (27), 222 (26), 254 (20) [M^++H]; **HRMS Calcd for** $C_{16}H_{15}NO_2$ 253.1103, found 253.1101 [M^+].

(4*S*,5*S*)-5-(1,2-dimethyl-1H-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 177k and 3-(1,2-dimethyl-1H-indol-3-yl)-4-methylphenol 178k



177k



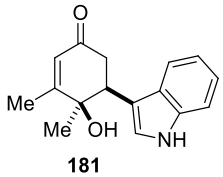
178k

Following the general procedure **I**, the reaction of *p*-quinol **3** (100 mg, 0.806 mmol), 1,2-dimethyl-1H-indole **176k** (128.6 mg, 0.887 mmol) and $FeCl_3{\cdot}6H_2O$ (21.8 mg, 0.0806 mmol) in CH_2Cl_2 (8 ml) gave a 60:40 mixture of **177k/178k**. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 27.6 mg (11% yield) of **178k** (less polar fraction) were obtained as a dark brown oil and 80.7 mg (30% yield) of **177k** (most polar fraction) were obtained pure as a brown oil. Reaction time: 20 hours.

Signals for **177k**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.77 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 10.1 Hz, 1H), 6.03 (d, *J* = 10.0 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.63 (s, 3H), 3.37 (dd, *J* = 13.5, 3.7 Hz, 1H), 2.43 – 2.36 (m, 1H), 2.30 (s, 3H), 1.24 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 200.74, 151.98, 137.12, 134.84, 129.16, 126.68, 120.88, 120.51, 119.48, 108.95, 108.11, 71.02, 43.05, 39.92, 29.76, 28.07, 10.85; **MS (ESI) *m/z* (%):** 292 (10) [M^++Na], 561 (17) [2M^++Na], 252 (36) [M^+-OH], 270 (100) [M^++H]; **HRMS Calcd for** $C_{17}H_{20}NO_2$ 270.1488, found 270.1485 [M^++H].

Signals for **178k**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = δ 7.37 (dd, *J* = 12.8, 8.1 Hz, 2H), 7.23 (d, *J* = 9.2 Hz, 2H), 7.09 (dd, *J* = 16.9, 7.6 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 1H), 3.77 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 151.69, 137.01, 135.17, 131.99, 129.30, 129.16, 126.94, 121.52, 120.63, 119.94, 118.86, 114.78, 108.90, 107.16, 29.80, 20.58, 11.00; **MS (EI) *m/z* (%):** 251 (100) [M^+], 250 (53), 252 (21), 248 (13), 249 (12); **HRMS Calcd for** $C_1H_{17}NO$ 251.1310, found 251.1304 [M^+].

(4*R*,5*S*)-4-hydroxy-5-(1H-indol-3-yl)-3,4-dimethylcyclohex-2-enone 181.

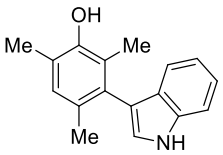


181

Following the general procedure **I**, the reaction of *p*-quinol **77** (147 mg, 1.06 mmol), 1*H*-indole **176a** (137.5 mg, 1.17 mmol) and $FeCl_3{\cdot}6H_2O$ (28.7 mg, 0.106 mmol) in CH_2Cl_2 (10 ml) gave **181** as the only product. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 188 mg (70% yield) of **181** were obtained as a brown solid. Reaction time: 18 hours.

M.p.: decomposes; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.30 (brs, 1H), 7.66 – 7.64 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.37 (d, *J* = 8.2 Hz, 1H), 7.26 – 7.13 (m, 2H), 7.04 – 7.03 (d, *J* = 2.5 Hz, 1H), 5.98 (s, 1H), 3.80 – 3.76 (t, *J* = 5.8 Hz, 1H), 2.97 – 2.89 (dd, *J* = 17.0 and 6.3 Hz, 1H), 2.88 – 2.80 (dd, *J* = 16.9 and 5.3 Hz, 1H), 2.02 (s, 3H), 1.57 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 198.4, 164.9, 135.8, 127.9, 126.7, 122.7, 122.3, 120.1, 119.1, 114.1, 111.3, 72.9, 43.1, 42.0, 26.3, 19.5; **MS (ESI) *m/z* (%):** 533 (18), 511 (27) [M^++Na], 256 (100) [M^++H]; **HRMS Calcd for** $C_{16}H_{18}NO_2$ 256.1332, found 256.1332 [M^++H].

3-(1H-indol-3-yl)-2,4,6-trimethylphenol 182.

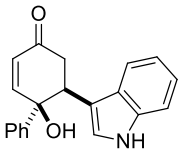


182

Following the general procedure **I**, the reaction of *p*-quinol **172** (90.1 mg, 0.59 mmol), 1*H*-indole **176a** (76.6 mg, 0.65 mmol) and $FeCl_3{\cdot}6H_2O$ (16 mg, 0.059 mmol) in CH_2Cl_2 (6 ml) gave **182** as the only product. After flash column chromatography (eluent Hex:AcOEt 4:1) 38.4 mg (26% yield) of **182** were obtained as a pink oil. Reaction time: 3 days.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (brs, 1H), 7.46 – 7.43 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.11 – 7.03 (m, 2H), 6.95 (s, 1H), 4.55 (bs, 1H), 2.31 (s, 3H), 2.01 (s, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 150.0, 135.9, 132. 6, 130.1, 129.1, 127.5, 123.5, 122.6, 121.9, 121.8, 119.9, 119.6, 116.0, 111.0, 20.2, 15.9, 13.5.; **MS (ESI) *m/z* (%):** 251 (100) [M^++H], 236 (70), 220 (31); **HRMS Calcd for** $C_{17}H_{17}NO$ 251.1310, found 251.1298 [M^+].

(1S,2S)-1-hydroxy-2-(1H-indol-3-yl)-2,3-dihydro-[1,1'-biphenyl]-4(1H)-one 184.

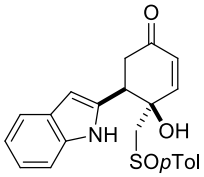


184

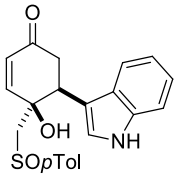
Following the general procedure **I**, the reaction of *p*-quinol **174** (104 mg, 0.56 mmol), 1*H*-indole **176a** (72 mg, 0.61 mmol) and $FeCl_3{\cdot}6H_2O$ (15 mg, 0.06 mmol) in CH_2Cl_2 (5.5 ml) gave **184** as the only product. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 30 mg (18% yield) of **184** were obtained as a brown oil. Reaction time: 3 hours.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (brs, 1H), 7.39 – 7.26 (m, 7H), 7.17 – 7.12 (t, *J* = 7.6 Hz, 1H), 7.08 – 7.06 (m, 1H), 6.97 – 6.92 (m, 1H), 6.92 – 6.88 (d, *J* = 10.2 Hz, 1H), 6.36 – 6.33 (d, *J* = 10.1 Hz, 1H), 4.02 – 3.98 (dd, *J* = 9.4 and 4.4 Hz, 1H), 3.12 – 3.04 (dd, *J* = 16.4 and 9.3 Hz, 1H), 2.76 – 2.69 (dd, *J* = 16.4 and 4.5 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$):** δ = 199.5, 151.6, 144.0, 135.7, 129.5, 128.4 (2C), 127.7, 127.4, 125.6 (2C), 122.9, 122.5, 119.9, 119.1, 113.4, 111.0, 74.2, 45.0, 41.0; **MS (ESI) *m/z* (%):**244 (100), 304 (67) [M^++H], 286 (41) [M^+-OH], 607 (9) [2M^++H], 326 (7) [M^++Na]; **HRMS Calcd for** $C_{20}H_{18}NO_2$ 304.1332, found 304.1343 [M^++H].

(4S,5S)-4-hydroxy-5-(1H-indol-3-yl)-4-((+)-(*R*)-*p*-tolylsulfinyl)-methyl)-cyclohex-2-enones (*R*,*R*,*R*)-185 and (*S*,*S*,*R*)-185



(*R*,*R*,*R*)-185



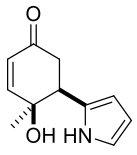
(*S*,*S*,*R*)-185

Following the general procedure **I**, the reaction of *p*-quinol **47** (50 mg, 0.19 mmol), 1*H*-indole **176a** (25 mg, 0.21 mmol) and $FeCl_3 \cdot 6H_2O$ (5.1 mg, 0.019 mmol) in CH_2Cl_2 (2 ml) gave a 70:30 diastereomeric mixture of **185** . After flash column chromatography (eluent Hex:AcOEt 2:1 - AcOEt) 70 mg (96% yield) of a 66:34 inseparable mixture of diastereoisomers **(*R*,*R*,*R*)-185/(*S*,*S*,*R*)-185** were obtained as a brown oil. Reaction time: 18 hours.

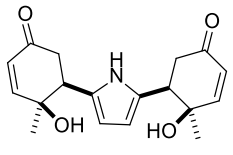
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (brs, 0.35H), 8.39 (brs, 0.5H), 7.68 – 7.63 (m, 1H), 7.41 – 7.36 (m, 3H), 7.26 – 7.22 (m, 4H), 7.21 – 7.09 (m, 2H), 6.20 – 6.17 (d, *J* = 10.2 Hz, 0.53H), 6.12 – 6.09 (d, *J* = 10.2 Hz, 0.27H), 4.16 – 4.02 (m, 1H), 3.23 – 3.10 (m, 2H), 2.98 – 2.94 (d, *J* = 13.6 Hz, 0.41H), 2.88 – 2.83 (d, *J* = 13.6 Hz, 0.5H), 2.76 – 2.66 (m, 1H), 2.37 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 199.3, 199.2, 150.3, 149.9, 142.0, 141.9, 140.1, 139.8, 135.8, 135.7, 130.1, 130.0, 129.3, 129.2, 127.5, 127.3, 124.1, 123.9, 123.6, 122.3, 119.8, 119.7, 118.7, 112.7, 111.6, 111.4, 71.3, 71.1, 66.4, 65.4, 41.4, 40.4, 21.3. **MS (ESI) *m/z* (%):** 222 (100), 380 (34) [M^++H], 402 (10) [M^++Na]; HRMS **Calcd for** $C_{22}H_{22}NO_3S$ 380.1314, found 380.1323 [M^++H].

<u>Reactions of π-excedent heteroaromatic derivatives to *p*-quinol 3</u>

(4S,5S)-4-hydroxy-4-methyl-5-(1H-pyrrol-2-yl)cyclohex-2-enone 187a and (4S,5S)-4-hydroxy-5-(5-((1R,2R)-2-hydroxy-2-methyl-5-oxocyclohex-3-en-1-yl)-1H-pyrrol-2-yl)-4-methylcyclohex-2-enone 188a



187a



188a

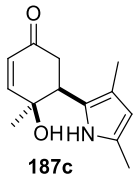
Following the general procedure **I**, the reaction of *p*-quinol **3** (20 mg, 0.16 mmol), pyrrole **186a** (12.3 µl, 0.18 mmol) and $FeCl_3 \cdot 6H_2O$ (4.3 mg, 0.016 mmol) in CH_2Cl_2 (1.6 ml) gave a 1:3 mixture of **187a/188a** from a complex mixture of reaction. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 1.6 mg (5% yield) of **187a** were obtained as a brown oil and 7.2 mg (28% yield) of **188a** were obtained as a brown oil. Reaction time: 1 hour.

Signals for **187a**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.52 (brs, 1H), 6.79 – 6.76 (m, 2H), 6.317 – 6.15 (m, 1H), 6.04 – 6.00 (m, 2H), 3.37 – 3.32 (dd, *J* = 10.6 and 4.3 Hz, 1H), 3.03 – 2.94 (dd, *J* = 16.7 and 10.6 Hz, 1H), 2.68 – 2.61 (dd, *J* = 16.8 and 4.3 Hz, 1H), 1.43 (s, 3H); **^{13}C NMR (75 MHz,**

$CDCl_3$): δ = 198.6, 152.5, 129.8, 128.8, 117.9, 108.3, 107.7, 69.6, 44.3, 40.8, 27.8; **MS (ESI) *m/z* (%):** 174 (100) [M^+-OH], 192 (51) [M^++H], 214 (87) [M^++Na]; **HRMS Calcd** for $C_{11}H_{14}NO_2$ 192.1019, found 192.1014 [M^++H].

Signals for **188a**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.86 (brs, 2H), 6.78 – 6.74 (d, *J* = 10.1 Hz, 2H), 6.02 – 5.99 (d, *J* = 10.0 Hz, 2H), 5.94 – 5.93 (d, *J* = 2.7 Hz, 2H), 3.32 – 3.28 (dd, *J* = 10.3 and 4.3 Hz, 2H), 2.99 – 2.90 (dd, *J* = 16.8 and 10.3 Hz, 2H), 2.67 – 2.60 (dd, *J* = 16.8 and 4.4 Hz, 2H), 1.42 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 198.6, 152.5, 130.0, 128.8, 107.6, 77.2, 69.5, 44.4, 40.7, 27.8; **MS (ESI) *m/z* (%):** 279 (100), 316 (84) [M^++H], 338 (38) [M^++Na]; **HRMS Calcd** for $C_{18}H_{22}NO$ 316.1543, found 316.1540 [M^++H].

(4*S*,5*S*)-5-(3,5-dimethyl-1H-pyrrol-2-yl)-4-hydroxy-4-methylcyclohex-2-enone 187c.

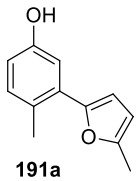


187c

Following the general procedure **I**, the reaction of *p*-quinol **3** (30 mg, 0.242 mmol), 2,4-dimethylpyrrole **186c** (27.4 µl, 0.266 mmol) and $FeCl_3 \cdot 6H_2O$ (6.5 mg, 0.0242 mmol) in CH_2Cl_2 (2.4 ml) gave **187c** as the only product. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 31.8 mg (60% yield) of **187c** were obtained as a brown oil. Reaction time: 45 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (brs, 1H), 6.84 – 6.80 (d, *J* = 10.1 Hz, 1H), 6.04 – 6.01 (dd, *J* = 10.1 and 0.9 Hz, 1H), 5.67 (d, *J* = 2.8 Hz, 1H), 3.33 – 3.28 (dd, *J* = 12.2 and 4.1 Hz, 1H), 2.97 – 2.88 (dd, *J* = 16.7 and 12.2 Hz, 1H), 2.57 – 2.50 (ddd, *J* = 16.8, 4.2 and 0.9 Hz, 1H), 2.21 (s, 3H), 1.98 (s, 3H), 1.38 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 199.9, 153.1, 128.6, 126.7, 124.4, 116.4, 107.4, 69.8, 40.9, 40.6, 27.4, 13.0, 10.9. **MS (ESI) *m/z* (%):** 461 (21) [2M^++Na], 202 (24) [M^+-OH], 242 (26) [M^++Na], 220 (100) [M^++H]; **HRMS Calcd** for $C_{13}H_{18}NO_2$ 220.1332, found 220.1333 [M^++H].

4-methyl-3-(5-methylfuran-2-yl)phenol 191a.



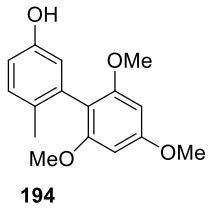
191a

Following the general procedure **I**, the reaction of *p*-quinol **3** (50 mg, 0.403 mmol), 2-methylfuran **190a** (40 µl, 0.43 mmol) and $FeCl_3 \cdot 6H_2O$ (11mg, 0.0403 mmol) in CH_2Cl_2 (4 ml) gave **191a** as the only product. After flash column chromatography (eluent Hex:AcOEt 5:1) 37.9 mg (50% yield) of **191a** were obtained as a brown oil. Reaction time: 1 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 – 7.21 (d, *J* = 2.7 Hz, 1H), 7.09 – 7.06 (d, *J* = 8.2 Hz, 1H), 6.69 – 6.66 (dd, *J* = 8.2 and 2.8 Hz, 1H), 6.44 – 6.43 (d, *J* = 3.2 Hz, 1H), 6.09 – 6.08 (d, *J* = 3.2 Hz,

1H), 5.13 (s, 1H), 2.40 (s, 3H), 2.37 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 153.6, 151.5, 151.2, 132.2, 131.3, 126.2, 113.9, 112.9, 109.8, 107.5, 21.1, 13.6. **MS (EI) *m/z* (%):** 189 (28) [M^++H], 145 (47), 188 (100) [M^+]; **HRMS Calcd for $C_{12}H_{12}O_2$** 188.0837, found 188.0828 [M^+].

2',4',6'-trimethoxy-6-methyl-[1,1'-biphenyl]-3-ol 194.



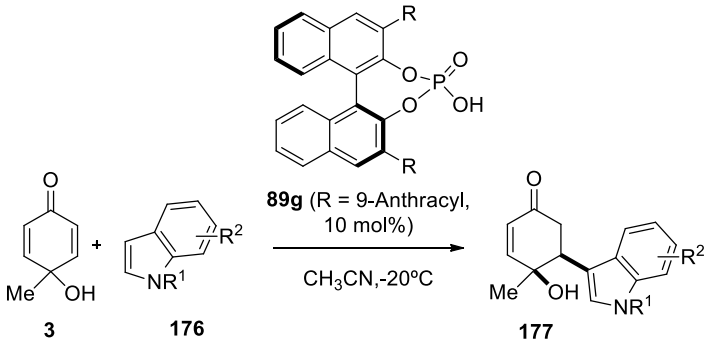
194

Following general procedure **I**, the reaction of *p*-quinol **3** (15 mg, 0.121 mmol, 1 equiv), 1,3,5-trimethoxybenzene **193** (22.3 mg, 0.133 mmol, 1.1 equiv) and $FeCl_3{\cdot}H_2O$ (3.3 mg, 0.0121 mmol, 10 mol%) in CH_2Cl_2 (1.2 ml) gave **194** as the only product. After flash column chromatography (eluent Hex:AcOEt 3:1) 6.7 mg (20% yield) of **194** were obtained as a brown oil. Reaction time: 5 days

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 – 7.10 (d, *J* = 8.2 Hz, 1H), 6.74 – 6.70 (dd, *J* = 8.2 and 2.8 Hz, 1H), 6.62 – 6.61 (d, *J* = 2.8 Hz, 1H), 6.22 (s, 2H), 3.87 (s, 3H), 3.70 (s, 6H), 2.17 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 160.7, 158.2, 152.9, 135.3, 130.4, 130.0, 118.1, 114.1, 111.5, 90.8, 55.8, 55.3, 30.9, 29.7, 18.8; **MS (EI) *m/z* (%):** 274 (91) [M^+], 243 (100); **HRMS Calcd for $C_{16}H_{18}O_4$** 274.1205, found 274.1197 [M^+].

General procedure for the enantioselective FC reaction of indoles to *p*-quinol 3.

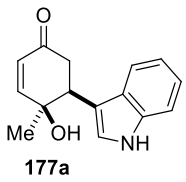
GENERAL PROCEDURE J



3 **176** **177**

A mixture of *p*-quinol **3** (1 equiv) and the indicated indole **176** (1.1 equiv) was dissolved in CH_3CN (0.1 M) at -20°C. Phosphoric acid **89g** (10 mol%) was then added and the mixture was stirring at -20°C for the time indicated in each case. Then, the crude mixture was washed with water and dried over anhydrous $MgSO_4$. The solvent was then removed under reduced pressure. The crude product was purified by flash chromatography using the eluent indicated in each case.

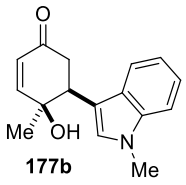
(4*S*,5*S*)-4-hydroxy-5-(1H-indol-3-yl)-4-methylcyclohex-2-enone 177a.



177a

Following the general procedure **J**, the reaction of *p*-quinol **3** (15 mg, 0.121 mmol), 1*H*-indole **176a** (15.6 mg, 0.133 mmol) and **89g** (8 mg, 0.0121 mmol) in CH_3CN (0.25 ml) gave **177a** as the only diastereoisomer. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 21 mg (72% yield) of **177a** were obtained as a dark green solid in a 72% *ee.* Reaction time: 6 days; **$[\alpha]_D^{20}$=** +9 (*c* 0.184 in $CHCl_3$).

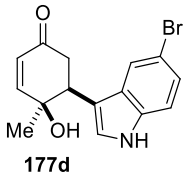
(4S,5S)-4-hydroxy-4-methyl-5-(1-methyl-1H-indol-3-yl)cyclohex-2-enone 177b



177b

Following the general procedure **J**, the reaction of *p*-quinol **3** (15 mg, 0.121 mmol), 1-methyl-indole **176b** (16.6 µl, 0.133 mmol) and **89g** (8 mg, 0.0121 mmol) in CH_3CN (0.25 ml) gave **177b** as the only diastereoisomer. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 15 mg (50% yield) of **177b** were obtained as a brown oil in a 8% *ee*. Reaction time: 6 days.

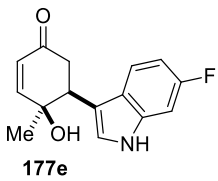
(4*S*,5*S*)-5-(5-bromo-1H-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 177d.



177d

Following the general procedure **J**, the reaction of *p*-quinol **3** (15 mg, 0.121 mmol), 5-bromo-1*H*-indole **176d** (26 mg, 0.133 mmol) and **89g** (8 mg, 0.0121 mmol) in CH_3CN (0.25 ml) gave **177d** as the only diastereoisomer. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 25.8 mg (67% yield) of **177d** were obtained as a brown solid in a 62% *ee.* Reaction time: 5 days; **$[\alpha]_D^{20}$=** +11 (*c* 0.051 in $CHCl_3$).

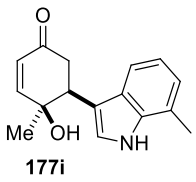
(4*S*,5*S*)-5-(6-fluoro-1H-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 177e.



177e

Following the general procedure **J**, the reaction of *p*-quinol **3** (15 mg, 0.121 mmol), 6-fluoro-1*H*-indole **176e** (18 mg, 0.133 mmol) and **89g** (8 mg, 0.0121 mmol) in CH_3CN (0.25 ml) gave **177e** as the only diastereoisomer. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 12.4 mg (40% yield) of **177e** were obtained as a brown oil in a 64% *ee*. Reaction time: 6 days; **$[\alpha]_D^{20}$=** +10 (*c* 0.082 in $CHCl_3$).

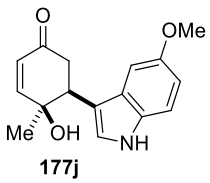
(4*S*,5*S*)-4-hydroxy-4-methyl-5-(7-methyl-1H-indol-3-yl)cyclohex-2-enone 177i



177i

Following the general procedure **J**, the reaction of *p*-quinol **3** (15 mg, 0.121 mmol), 7-methyl-1*H*-indole **176i** (17.5 mg, 0.133 mmol) and **89g** (8 mg, 0.0121 mmol) in CH_3CN (0.25 ml) gave **177i** as the only diastereoisomer. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 18.3 mg (60% yield) of **177i** were obtained as a green solid in a 52% *ee*. Reaction time: 6 days; $\mathbf{[\alpha]_D^{20}=}$ +20 (*c* 0.0702 in $CHCl_3$).

(4*S*,5*S*)-4-hydroxy-5-(5-methoxy-1H-indol-3-yl)-4-methylcyclohex-2-enone 177j

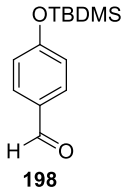


177j

Following the general procedure **J**, the reaction of *p*-quinol **3** (15 mg, 0.121 mmol), 5-methoxy-1*H*-indole **176j** (19.6 mg, 0.133 mmol) and **93g** (8 mg, 0.0121 mmol) in CH_3CN (0.25 ml) gave **177j** as the only diastereoisomer. After flash column chromatography (eluent Hex:AcOEt 3:1 - AcOEt) 16.6 mg (50% yield) of **177j** were obtained as a brown oil in a 62% *ee*. Reaction time: 6 days; $\mathbf{[\alpha]_D^{20}=}$ +2 (*c* 0.21 in $CHCl_3$).

EXPERIMENTAL PART OF CHAPTER 3.2: Intramolecular FC reactions of 4-(2-indolylalkyl)quinols.

4-((*tert*-butyldimethylsilyl)oxy)benzaldehyde 198.[130]

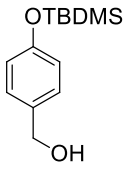


198

A solution of *tert*-butyldimethylsilylchloride (6.8 g. 45.0 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to a solution of 4-hydroxybenzaldehyde **197** (3.7 g, 30.0 mmol) and triethylamine (6.3 mL, 45.0 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water (150 mL) and brine (150 mL), dried over MgSO4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 9:1) to afford 4-((tert-butyldimethylsilyl)oxy)benzaldehyde **198** as a yellow oil (6.5 g, 91% yield).

^{1}H NMR (300 MHz, $CDCl_3$):[130] δ = 9.89 (s, 1H), 7.80 – 7.77 (d, *J* = 8.6 Hz, 2H), 6.96 – 6.93 (d, *J* = 8.8 Hz, 2H), 1.00 (s, 9H), 0.25 (s, 6H).

4-((*tert*-butyldimethylsilyl)oxy)benzylalcohol 199.[131]

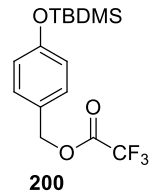


199

Benzaldehyde **198** (6.18 g, 26.2 mmol) was dissolved in MeOH (60 ml, 0.45 M) and cooled to 0°C. Sodium borohydride (1.19 g, 31.4 mmol) was added slowly with stirring. After 10 min at 0°C, the remaining sodium boronhydride was destroyed with small amounts of water, extracted with AcOEt, dried over $MgSO_4$ and concentrated in vacuo to afford the corresponding benzyl alcohol **199** without further purification (4.36 g, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$):[152] δ = 7.24 – 7.21 (d, *J* = 8.4 Hz, 2H), 6.84 – 6.81 (d, *J* = 8.4 Hz, 2H), 4.61 (s, 2H), 0.98 (s, 9H), 0.19 (s, 6H).

4-((*tert*-butyldimethylsilyl)oxy)benzyl trifluoroacetate 200.[131]



200

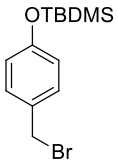
Benzylalcohol **199** (4.5 g, 18.9 mmol) was dissolved in dry THF (12 mL, 0.84 M), trifluoroacetic acid anhydride (3 mL, 21.7 mmol) was slowly added with stirring and the mixture was heated to reflux for 1 hour. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (10 mL) and washed

[152] Kopka, K.; Faust, A., Keul, P.; Wagner, S.; Breyholz, H.-J.; Höltke, C.; Schobe, O.; Schäfers, M.; Levkau, B. *J. Med. Chem.* **2006**, *49*, 6704.

with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford **200** as a pale yellow oil without further purification (5.5 g, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$):[131] δ = 7.29 – 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 – 6.84 (d, *J* = 8.5 Hz, 2H), 5.29 (s, 2H), 1.00 (s, 9H), 0.22 (s, 6H).

4-((*tert*-butyldimethylsilyl)oxy)benzylbromide 201.[131]

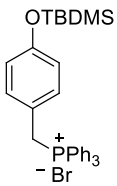


201

Benzyl trifluoroacetate **200** (1.8 g, 5.3 mmol) was dissolved in dry THF (7 mL, 0.8 M) and dry lithium bromide (572 mg, 6.6 mmol) was added with stirring. The mixture was heated to reflux for 20 h, cooled, diluted with acetonitrile (10 mL) and extracted three times with hexane. The hexane layers were combined and concentrated in vacuo to affording **201** as a yellow oil without further purification (1.42 g, 90% yield).

^{1}H NMR (300 MHz, $CDCl_3$):[131] δ = 7.27 – 7.24 (d, *J* = 8.0 Hz, 2H), 6.80 – 6.78 (d, *J* = 8.5 Hz, 2H), 4.49 (s, 2H), 0.98 (s, 9H), 0.20 (s, 2H).

(4-((*tert*-butyldimethylsilyl)oxy)benzyl)triphenylphosphonium bromide 202.[132]



202

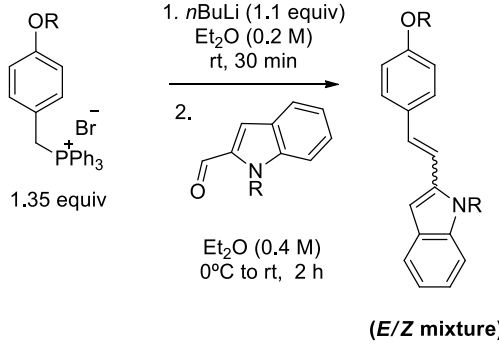
Benzyl bromide **201** (3.6 g, 7.7 mmol) was dissolved in toluene (5.5 mL, 1.4 M) and PPh_3 (2.23 g, 8.5 mmol) was added. The reaction mixture was stirred at reflux for 18 hours. After completion, the reaction was cooled to room temperature, filtrated, and the solid was washed with toluene followed by hexane, to give the corresponding phosphonium bromide salt **202** without further purification (3.8 g, 87% yield).

^{1}H NMR (300 MHz, Acetone-d_6):[153] δ = 7.97 – 7.90 (m, 9H), 7.81 – 7.77 (m, 6H), 7.15 – 7.12 (m, 2H), 6.77 – 6.74 (d, *J* = 8.4 Hz, 2H), 5.54 – 5.49 (d, J_{HP} = 14.5 Hz, 2H), 1.00 (s, 9H), 0.22 (s, 6H).

[153] Olszewski, J. D.; Marshalla, M.; Sabat, M.; Sundberg, R. J. *J. Org.Chem.* **1994**, *59*, 4285

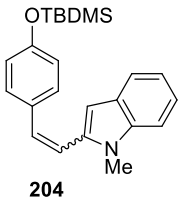
General procedure for the synthesis of vinyl indole derivatives

GENERAL PROCEDURE K:[133]



To a suspension of the corresponding phosphonium bromide (1.35 equiv) in Et_2O (0.2 M) was added a solution of *n*-BuLi (1.1, 2.5 M in hexanes) at rt under an argon atmosphere. The resulting mixture was stirred at rt for 30 min and then cooled to 0 °C. A solution of indole-2-carbaldehyde (1 equiv) in Et_2O (0.4 M) was added to the mixture over a period of 10 min. After the addition was completed, the mixture was allowed to warm to rt and was stirred during 2 hours. Water was added to the reaction mixture, and the resulting mixture was extracted with AcOEt (x3). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography affording the corresponding *E/Z* mixture of vinyl indole derivatives.

***E/Z*-2-(4-((*tert*-butyldimethylsilyl)oxy)styryl)-1-methyl-1H-indole 204.**



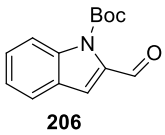
204

Following the general procedure **K**, to a suspension of phosphonium bromide **202** (1.97 g, 3.5 mmol) in Et_2O (17 ml) was added a solution of *n*-BuLi (1.56 ml, 3.9 mmol, 2.5 M in hexanes) at rt under an argon atmosphere. The resulting mixture was stirred at rt for 30 min and then cooled to 0 °C. A solution of 1-methyl-1H-indole-2-carbaldehyde **203** (414 mg, 2.6 mmol) in Et_2O (6 ml) was added to the mixture over a period of 10 min. After the addition was completed, the mixture was allowed to warm to rt and was stirred during 2 hours. After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 9:1) to afford **204** as a 77:33 mixture of ***E/Z*** as a yellow oil (1.91 g, 73% yield).

Signals for **204** ***(E/Z):*** **^{1}H NMR (300 MHz, $CDCl_3$):** δ =7.68 - 6.53 (m, 1H), 3.85 (s, 2.2H), 3.61 (s, 0.6H), 1.09 (s, 6.8H), 1.06 (s, 1.6H), 0.31 (s, 4.3H), 0.25 (s, 1.4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 155.7, 155.3, 138.8, 138.0, 137.2, 136.7, 133.8, 133.0, 130.7, 130.5, 130.1, 129.9, 128.4, 128.0,

128.0, 127.6, 127.5, 121.5, 121.3, 120.4, 120.4, 120.2, 120.1, 119.9, 119.8, 119.5, 117.5, 115.1, 109.2, 109.0, 101.2, 98.4, 30.0, 29.8, 29.7, 25.7, 25.6, 18.2, 18.2, -4.4, -4.4; **Minor isomer: MS (EI) *m/z* (%):** 363 (100) [M^+], 364 (38) [M^++H]; **HRMS Calcd for** $C_{23}H_{29}NOSi$ 363.2018, found 363.2018 [M^+]; **Major isomer: MS (EI) *m/z* (%):** 363 (100) [M^+], 364 (38) [M^++H]; **HRMS Calcd for** $C_{23}H_{29}NOSi$ 363.2018, found 363.2033 [M^+].

***tert*-butyl 2-formyl-1H-indole-1-carboxylate 206.**[134]

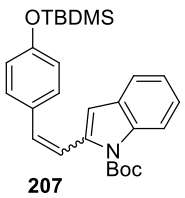


206

To a stirred solution of 1H-indole-2-carbaldehyde **205** (1 g, 6.9 mmol) and di-*tert*-butyl dicarbonate (1.9 g, 8.8 mmol) in acetonitrile (13 mL) was added DMAP (84 mg, 0.7 mmol). The resulting solution was stirred 2.5 hours and then the solvent was removed under reduced pressure. The solid residue was then dissolved in dichloromethane (40 mL) and washed with saturated sodium hydrogen carbonate solution (40 mL). The aqueous was then extracted with dichloromethane (40 mL) and then the combined organic extracts were washed with saturated ammonium chloride solution (60 mL), water (60 mL) and brine (60 mL) and then dried ($MgSO_4$) and concentrated in vacuo to yield the desired product **206** as a pink solid (1.6 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$):[154] δ = 10.28 (s, 1H), 8.03 – 8.00 (m, 1H), 7.52 - 7.49 (m, 1H), 7.39 – 7.26 (m, 1H), 7.20 – 7.08 (m, 1H), 1.57 (s, 9H).

***tert*-butyl 2-(4-((tert-butyldimethylsilyl)oxy)styryl)-1H-indole-1-carboxylate 207.**



207

Following the general procedure **K**, to a suspension of phosphonium bromide **202** (3 g, 5.3 mmol) in Et_2O (19 ml) was added a solution of *n*-BuLi (2.37 ml, 5.9 mmol, 2.5 M in hexanes) at rt under an argon atmosphere. The resulting mixture was stirred at rt for 30 min and then cooled to 0 °C. A solution of *tert*-butyl-2-formyl-1H-indole-1-carboxylate **206** (963 mg, 3.9 mmol) in Et_2O (9.2 ml) was added to the mixture over a period of 10 min. After the addition was completed, the mixture was allowed to warm to rt and was stirred during 2 hours. After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 9:1) to afford **207** as a mixture 69:31 of ***E/Z*** as a yellow oil (2.2 g, 92% yield).

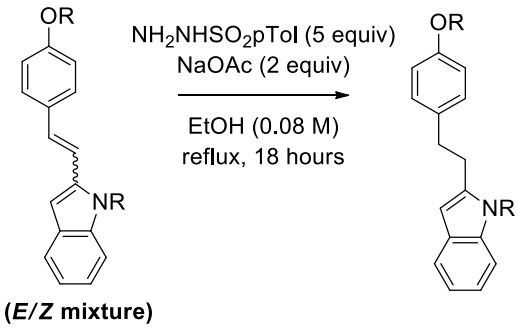
Signals for **207 *(E/Z):* ^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.98 – 7.92 (m, 1H), 7.46 – 7.40 (m, 0.72H), 7.35 – 7.32 (m, 0.73H), 7.25 – 7.22 (m, 1.52H), 7.19 – 7.16 (m, 0.74H), 7.08 – 7.00 (m, 2.69H),

[154] Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5840.

6.85 – 6.80 (m, 0.72H), 6.68 – 6.63 (m, 2.08H), 6.53 – 6.48 (m, 0.92H), 6.41 – 6.37 (m, 0.33H), 6.26 (s, 0.30H), 1.53 (s, 5.89H), 1.49 (s, 2.59H), 0.83 (s, 6.11H), 0.79 (s, 3.02H), 0.05 (s, 4.01H), -0.00 (s, 1.88H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 155.7, 155.1, 150.8, 150.5, 140.1, 137.0, 136.9, 136.2, 130.8, 130.4, 130.3, 130.2, 129.6, 129.6, 128.0, 124.1, 124.0, 123.1, 122.9, 121.0, 120.5, 120.5, 120.3, 120.0, 118.9, 115.8, 115.6, 109.4, 106.1, 84.0, 28.4, 28.3, 25.8, 25.8, 18.4, 18.3, -4.2, -4.3; **Minor isomer: MS (EI) *m/z* (%):** 292 (69), 293 (22), 349 (100) [M^+-Boc]. HRMS Calcd for $C_{22}H_{27}NOSi$ 349.1862, found 349.1876 [M^+-Boc]; **Major isomer: MS (EI) *m/z* (%):** 293 (42), 292 (100), 349 (98) [M^+-Boc]. HRMS Calcd for $C_{22}H_{27}NOSi$ 349.1862, found 349.1859 [M^+-Boc].

General procedure for the synthesis of 4-(2-indolyl)ethyl TBDMS *O*-protected phenols

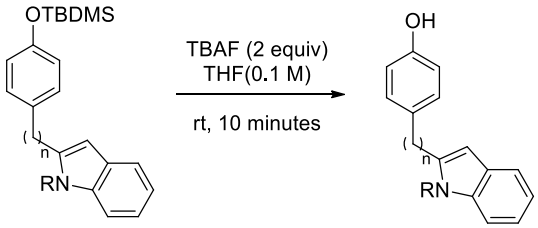
GENERAL PROCEDURE L[135]



NaOAc (2 equiv) and 4-methylbenzenesulfonehydrazide (5 equiv) were added to the solution of the corresponding E/Z mixture of vinyl indole derivative (1 equiv) in EtOH (0.08 M) under nitrogen and refluxed for 18 hours. When the starting material was consumed, water (13 mL) was added to the cooled reaction mixture; EtOH was evaporated under reduced pressure and extracted the suspension with EtOAc (3 × 10 mL). Organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography affording the corresponding reduced derivatives.

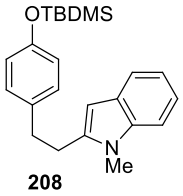
General procedure for the TBDMS deprotection

GENERAL PROCEDURE M[155]



A solution of tetrabutylammonium fluoride (TBAF) (2 equiv, 1 M in THF) was added dropwise to the corresponding OTBDMS protected phenol (1 equiv) in THF (0.1 M) at rt. The mixture was then kept at room temperature for 10 minutes and the solvent was concentrated under reduced pressure. AcOEt (6 mL) was added to the residue, and the resulting solution was washed with aqueous saturated $NaHCO_3$ (6 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography affording the corresponding phenols.

2-(4-((*tert*-butyldimethylsilyl)oxy)phenethyl)-1-methyl-1H-indole 208.



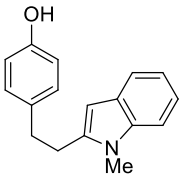
208

Following the general procedure **L**, NaOAc (430 mg, 5.25 mmol) and 4-methylbenzenesulfonohydrazide (988 mg, 5.25 mmol) were added to the solution of **204** (366 mg, 1.05 mmol) in EtOH (13 mL) under nitrogen and refluxed for 18 hours. After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 9:1) to afford **208** as yellow oil (225 mg, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 – 7.53 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.19 – 7.13 (m, 1H), 7.10 – 7.05 (m, 3H), 6.78 – 6.75 (d, *J* = 7.9 Hz, 2H), 6.30 (s, 1H), 3.60 (s, 3H), 0.99 (s, 9H), 0.19 (s, 6H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 153.9, 140.5, 137.2, 133.9, 129.2 (2C), 127.9, 120.5, 120.0 (2C), 119.8, 119.2, 108.68, 98.8, 34.4, 29.2, 29.0, 25.7 (3C), 18.2, -4.5 (2C); **MS (ESI) *m/z* (%):** 221(100), 144 (85), 365 (49) [M^+]; **HRMS Calcd for** $C_{23}H_{31}NOSi$ 365.2175, found 365.2187 [M^+].

[155] Katoh, T.;, Akagi, T.;, Noguchi, C.; Kajimoto.T.;, Node, M.; Tanaka, R.; Nishizawa, (née Iwamoto), M.; Ohtsu, H.; Suzukic; N.; Saitoc, K. *Bioorg. Med. Chem*. **2007**, *15*, 2736.

4-(2-(1-methyl-1H-indol-2-yl)ethyl)phenol 209.

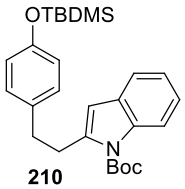


209

Following the general procedure **M**, a solution of tetrabutylammonium fluoride (TBAF) (1.3 mL, 1.3 mmol, 1 M in THF) was added dropwise to **208** (225 mg, 0.6 mmol) in THF (6 mL) at rt. The mixture was then kept at room temperature for 10 minutes and the solvent was concentrated under reduced pressure. After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 5:1) to afford **209** as a pale yellow oil (150 mg, 93% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.45 (d, *J* = 7.8 Hz, 1H), 7.18 – 7.13 (t, *J* = 7.5 Hz, 1H), 7.10 – 7.05 (m, 1H), 7.02 – 6.97 (m, 3H), 6.66 – 6.63 (d, *J* = 8.4 Hz, 2H), 6.21 (s, 1H), 4.82 (s, 1H), 3.49 (s, 3H), 2.89 (s, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 153.9, 140.6, 137.3, 133.5, 129.4 (2C), 127.8, 120.6, 119.8, 119.2, 115.3 (2C), 108.8, 98.8, 34.3, 29.3, 29.1; **MS (EI) *m/z* (%):** 251 (13) [M^+], 144 (100); **HRMS Calcd for** $C_{17}H_{17}NO$ 251.1310, found 251.1301 [M^+].

***tert*-butyl-2-(4-((tert-butyldimethylsilyl)oxy)phenethyl)-1H-indole-1 carboxylate 210**

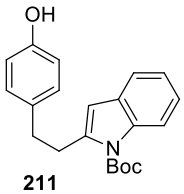


210

Following the general procedure **L**, NaOAc (1.62 g, 19.7 mmol) and 4-methylbenzenesulfonohydrazide (3.7 g, 19.7 mmol) were added to the solution of **207** (1.32 g, 3.9 mmol) in EtOH (49 mL) under nitrogen and refluxed for 18 hours .After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 9:1) to afford **210** as a colorless oil (705 mg, 67% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 – 7.87 (m, 1H), 7.27 – 7.21 (m, 1H), 7.10 – 6.94 (m, 2H), 6.91 – 6.88 (d, *J* = 8.4 Hz, 2H), 6.59 – 6.56 (d, *J* = 8.5 Hz, 2H), 6.13 (s, 1H), 3.14 – 3.07 (m, 2H), 2.80 – 2.73 (m, 2H), 1.50 (s, 9H), 0.80 (s, 9H), -0.00 (s, 6H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ = 153.8, 150.6, 141.7, 136.6, 134.3, 129.4, 129.3(2C), 123.3, 122.6, 120.0(2C), 120.0, 116.0, 107.4, 83.8, 34.5, 32.1, 28.3(3C), 25.8(3C), 18.3, -4.4(2C); **MS (ESI) *m/z* (%):** 452 (78) [M^++H], 474 (100) [M^+ + Na], 349 (100) [M^+ + H]. **HRMS Calcd for** $C_{27}H_{38}NO_3Si$ 452.2615, found 452.2620 [M^+ + H].

***tert*-butyl 2-(4-hydroxyphenethyl)-1H-indole-1-carboxylate 211.**



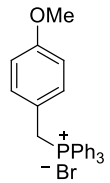
211

Following the general procedure **M**, a solution of tetrabutylammonium fluoride (TBAF) (2.8 mL, 2.8 mmol, 1 M in THF) was added dropwise to **210** (610 mg, 1.4 mmol) in THF (14 mL) at rt. The mixture was then kept at room

temperature for 10 minutes and the solvent was concentrated under reduced pressure. After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 5:1) to afford **211** as a pale pink solid (415 mg, 88% yield).

M.p: 128 – 131°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.15 – 8.13 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.48 (dd, *J* = 7.0 and 1.3 Hz, 1H), 7.32 – 7.21 (m, 2H), 7.14 – 7.11 (d, *J* = 8.6 Hz, 2H), 6.81 – 6.78 (d, *J* = 8.6 Hz, 2H), 6.39 (s, 1H), 5.38 (bs, 1H), 3.37 – 3.32 (m, 2H), 3.02 – 2.97 (m, 2H), 1.73 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 153.76, 150.65, 141.64, 136.46, 133.54, 129.41 (2C), 129.29, 123.27, 122.59, 119.78, 115.52, 115.19 (2C), 107.42, 83.88, 34.26, 31.95, 28.22 (3C); **MS (ESI) *m/z* (%):** 282 (100), 338 (25) [M^+ + H], 360 (44) [M^+ + Na]. **HRMS Calcd for** $C_{21}H_{24}NO_3$ 338.1750, found 338.1757 [M^+ + H].

(4-methoxybenzyl)triphenylphosphonium bromide 213.

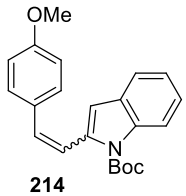


213

Commercially available benzyl bromide **212** (3.6 g, 7.7 mmol) was dissolved in toluene (5.5 mL, 1.4 M) and PPh_3 (2.23 g, 8.5 mmol) was added. The reaction mixture was stirred at reflux for 18 hours. After completion, the reaction was cooled to room temperature, filtrated, and the solid was washed with toluene followed by hexane, to give the corresponding phosphonium bromide salt **213** without further purification (3.5 g, 98% yield).

^{1}H NMR (300 MHz, $CDCl_3$):[156] δ = 7.81 – 7.44 (m, 15H), 6.94 – 6.91 (dd, *J* = 8.8 and 6.0 Hz, 2H), 6.58 – 6.55 (d, *J* = 8.6 Hz, 2H), 5.14 - 5.09 (d, J_{HP} = 13.7 Hz, 2H), 3.64 (s, 3H).

***tert*-butyl 2-(4-methoxystyryl)-1H-indole-1-carboxylate 214.**



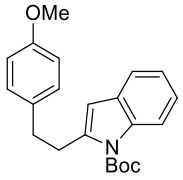
214

Following the general procedure **K**, to a suspension of phosphonium bromide **213** (951 mg, 2.1 mmol) in Et_2O (7.2 ml) was added a solution of *n*-BuLi (0.91 ml, 2.3 mmol, 2.5 M in hexanes) at rt under an argon atmosphere. The resulting mixture was stirred at rt for 30 min and then cooled to 0 °C. A solution of *tert*-butyl-2-formyl-1H-indole-1-carboxylate **206** (373 mg, 1.5 mmol) in Et_2O (3.5 ml) was added to the mixture over a period of 10 min. After the addition was completed, the mixture was allowed to warm to rt and was stirred during 2 hours. After the corresponding isolation procedure, the crude product was used without further purification affording **214** as a 69:31 mixture of ***E/Z*** as yellow oil (532 mg, 99% yield).

[156] Chalal, M.; Vervandier-Fasseur, D.; Meunier, P.; Cattey, H.; Hierso, J.-C. *Tetrahedron* **2012**, *68*, 3899.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 – 6.36 (m, 11H), 3.74 (s, 1.89H), 3.67 (s, 0.98H), 1.61 (s, 5.15H), 1.58 (s, 2.80H).

***tert*-butyl 2-(4-methoxyphenethyl)-1H-indole-1-carboxylate 215.**

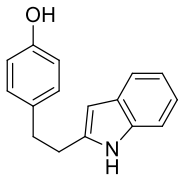


215

Following the general procedure **L**, NaOAc (624 mg, 7.61 mmol) and 4-methylbenzenesulfonohydrazide (850 mg, 4.57 mmol) were added to the solution of **214** (532 mg, 1.5 mmol) in EtOH (16 mL) under nitrogen and refluxed for 18 hours .After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 4:1) to afford **215** as a beige solid (160 mg, 30% yield).

M.p.: 121-123°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.18 – 8.15 (dd, *J* = 8.0 and 0.5 Hz, 1H), 7.52 – 7.50 (dd, *J* = 7.2 and 1.2 Hz, 1H), 7.34 – 7.24 (m, 2H), 7.23 – 7.21 (d, *J* = 8.6 Hz, 2H), 6.92 – 6.89 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 3.85 (s, 3H), 3.39 (m, 2H), 3.02 (m, 2H), 1.75 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 157.9, 150.5, 141.7, 136.5, 133.6, 129.3 (2C), 129.3, 123.2, 122.5, 119.8, 115.5, 113.8 (2C), 107.4, 83.7, 55.2, 34.3, 32.0, 28.2 (3C); **MS (ESI) *m/z* (%):** 296 (100), 252 (96), 352 (30) [M^++H], 374 (66) [M^+ + Na]; **HRMS Calcd for** $C_{22}H_{26}NO_3$ 352.1907, found 352.1914 [M^+ + H].

***tert*-butyl 2-(4-methoxyphenethyl)-1H-indole-1-carboxylate 216.**[137]

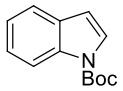


216

To a solution of **215** (40 mg, 0.11 mmol) in CH_2Cl_2 (1.14 ml), a solution of BBr_3 is added dropwise at 0 °C under atmosphere of Argon. After stirring at room temperature for 21 hours the reaction mixture was cooled to 0 °C and water is added and it was extracted with CH_2Cl_2 (3x2 ml) affording 30.5 mg of **216** (>99%) without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (brs, 1H), 7.54 – 7.52 (d, *J* = 7.2 Hz, 1H), 7.26 – 7.24 (d, *J* = 5.8 Hz, 1H), 7.14 – 7.05 (m, 4H), 6.78 – 6.75 (d, *J* = 8.5 Hz, 2H), 6.26 (s, 1H), 5.05 (brs, 1H), 3.04 – 2.94 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 154.0, 139.1, 135.8, 133.3, 129.5 (2C), 128.7, 121.0, 119.8, 119.6, 115.4 (2C), 110.3, 99. 8, 34.7, 30.4; **MS (FAB) *m/z* (%):** 55.1 (100), 237 (12) [M^+]. **HRMS Calcd for** $C_{16}H_{15}NO$ 237.1154, found 237.1150 [M^+].

***tert*-butyl 1H-indole-1-carboxylate 253** [134]

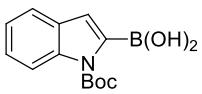


217

To a stirred solution of 1H-indole **168a** (2 g, 17.1 mmol) and di-*tert*-butyl dicarbonate (4.8 g, 22 mmol) in acetonitrile (33 mL) was added DMAP (210 mg, 1.7 mmol). The resulting solution was stirred 3.5 hours and then the solvent was removed under reduced pressure. The solid residue was then dissolved in dichloromethane (40 mL) and washed with saturated sodium hydrogen carbonate solution (40 mL). The aqueous was then extracted with dichloromethane (40 mL) and then the combined organic extracts were washed with saturated ammonium chloride solution (60 mL), water (60 mL) and brine (60 mL) and then dried ($MgSO_4$) and concentrated in vacuo to yield the desired product **217** as a brown oil (3.7 g, 97%).

^{1}H NMR (300 MHz, $CDCl_3$):[134] δ = 8.17 – 8.14 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.59 (d, *J*= 3.8 Hz, 1H), 7.58 – 7.55 (dd, *J* = 7.5 y 0.8 Hz, 1H), 7.34 – 7.28 (td, *J* = 7.5 y 1.4 Hz, 1H), 7.25 – 7.20 (td, *J* = 7.4 y 1.1 Hz, 1H), 6.58 – 6.56 (dd, *J* = 3.8 y 0.8 Hz, 1H), 1.68 (s, 9H).

(1-(*tert*-butoxycarbonyl)-1H-indol-2-yl)boronic acid 218.[138]

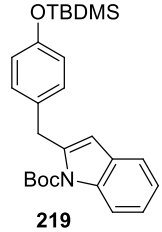


218

To a solution of *N*-Boc-indole **217** (1 g, 4.58 mmol) in THF (6 mL) was added triisopropylborate (1.6 mL, 6.9 mmol). The solution was cooled to 0 – 5 °C in an ice bath and LDA (6.24 ml, 1.36 mmol, 1 M) was added over 1 hr. After 30 min the reaction was quenched by the addition of 2N HCl. The organic layer was separated, the aqueous layer was extracted with AcOEt (x3), dried over $MgSO_4$ and concentrated in vacuo affording 980 mg (81%) of **218** as brown solid which was used without further purification.

^{1}H NMR (300 MHz, DMSO-d_6):[138] δ = 8.16 (s, 2H), 8.08 – 8.06 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.54 (d, *J* = 7.7 Hz, 1H), 7.29 – 7.24 (t, *J* = 7.6 Hz, 1H), 7.20 – 7.15 (t, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 1.59 (s, 9H); **^{11}B NMR (96 MHz, $CDCl_3$):** δ = 26.65.

***tert*-butyl-2-(4-((tert-butyldimethylsilyl)oxy)benzyl)-1H-indole-1-carboxylate 219.**[139]



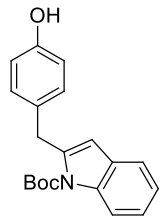
219

To a 10 mL vial containing a stir bar was added *N*-Boc-indole-2-boronic acid **218** (100 mg, 0.38 mmol), benzyl bromide **201** (82 mg, 0.27 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) followed by the addition of anhydrous/degassed DME (2.5 mL). The reaction mixture was diluted with 5.0 M Na_2CO_3 degassed aqueous solution (0.25 mL) to form a biphasic reaction

mixture that was warmed to 60 °C and allowed to stir for 18 hours. Then, the reaction was cooled to room temperature and diluted with water (10 mL). The resulting solution was extracted with EtOAc (3 x 3 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford the crude product as colorless oil. The residue was purified by flash column chromatography on silica gel (eluent Hex:AcOEt 20:1) affording 93.4 mg of a mixture 65:35 of **219/217** (51% yield of **255**).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 – 7.91 (d, *J* = 8.5 Hz, 1H), 7.24 – 7.21 (d, *J* = 7.3 Hz, 1H), 7.05 – 6.96 (m, 2H), 6.87 – 6.84 (d, *J* = 8.2 Hz, 2H), 6.61 – 6.58 (d, *J* = 8.5 Hz, 2H), 5.93 (s, 1H), 4.10 (s, 2H), 1.39 (s, 9H), 0.80 (s, 9H), 0.00 (s, 6H).

***tert*-butyl 2-(4-hydroxybenzyl)-1H-indole-1-carboxylate 220.**

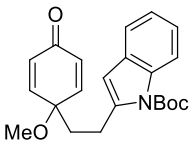


220

Following the general procedure **L**, a solution of tetrabutylammonium fluoride (TBAF) (0.28 mL, 0.28 mmol, 1 M in THF) was added dropwise to **219** (61 mg, 0.14 mmol) in THF (1.4 mL) at rt. The mixture was then kept at room temperature for 10 minutes and the solvent was concentrated under reduced pressure. After the corresponding isolation procedure, the crude product was purified by flash column chromatography (eluent Hex:AcOEt 5:1) to afford **220** as a white solid (37 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 – 8.09 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.40 (d, *J* = 7.3 Hz, 1H), 7.27 – 7.17 (m, 2H), 7.09 – 7.06 (d, *J* = 8.5 Hz, 2H), 6.80 – 6.77 (d, *J* = 8.6 Hz, 2H), 6.11 (s, 1H), 4.68 (s, 1H). 4.29 (s, 2H), 1.60 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 154.0, 150.5, 141.0, 136.8, 131.2, 130.1 (2C), 129.1, 123.4, 122.6, 119.9, 115.5, 115.2 (2C), 109.1, 83.9, 35.4, 28.1 (3C). MS (ESI) *m/z* (%): 324 (49) [M^++H], 346 (62) [M^++Na], 268 (86), 61 (100). HRMS Calcd for $C_{20}H_{22}NO_3$ 324.1594, found 324.1604 [M^++ H].

***tert*-butyl-2-(2-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl)-1H-indole-1-carboxylate 221.**

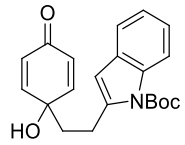


221

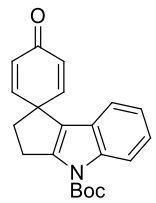
To a solution of **211** (685 mg, 2 mmol) in MeOH (20 ml) at 0°C was added PIDA (773 mg, 2.4 mmol) and the mixture was stirred at 0°C for 2 hours. MeOH was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent Hex:AcOEt 6:1) to afford **221** as a yellow oil (338 mg, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 – 8.04 (d, *J* = 7.9 Hz, 1H), 7.45 – 7.43 (d, *J* = 6.9 Hz, 1H), 7.26 – 7.15 (m, 2H), 6.85 – 6.81 (d, *J* = 10.2 Hz, 2H), 6.44 – 6.41 (d, *J* = 10.2 Hz, 2H), 6.32 (s, 1H), 3.26 (s, 3H), 3.02 – 2.96 (m, 2H), 2.19 – 2.13 (m, 2H), 1.65 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 185.3, 150.6 (2C), 150.3, 140.8, 136.5, 131.8 (2C), 129.1, 123.5, 122.7, 119.8, 115.5, 107.1, 83.9, 75.4, 53.0, 38.4, 28.2 (3C), 24.4; **MS (EI) *m/z* (%):** 268 (100), 368 (26) [M^++H], 390 (14) [M^++Na]. **HRMS Calcd for** $C_{22}H_{26}NO_4$ 368.1856, found 368.1860 [M^++H].

***tert*-butyl 2-(2-(1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl)-1H-indole-1-carboxylate 222 and *tert*-butyl 4-oxo-2'H-spiro[cyclohexa[2,5]diene-1,1'-cyclopenta[b]indole]-4'(3'H)-carboxylate 223.**



222



223

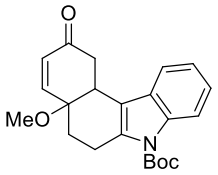
To a solution of **211** (170 mg, 0.5 mmol) in a 1:1 mixture of H_2O/CH_3CN (2.5 ml/ 2.5 ml) at 0°C was added PIDA (211 mg, 0.65 mmol) and the mixture was stirred at 0°C for 2 hours. The crude product was extracted with AcOEt (3 x 2 ml) and the resulting organic phase was dried over Na_2SO_4 and evaporated under reduced pressure affording a mixture 59:41 of **222/223**. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 6:1) to afford **222** as a yellow oil (85 mg, 48% yield) and **223** as a yellow oil (13 mg, 8%).

Signals for **222: ^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.04 – 8.01 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.43 (d, *J* = 7.7 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.94 – 6.91 (d, *J* = 9.7 Hz, 2H), 6.35 (s, 1H), 6.25 – 6.22 (d, *J* = 9.9 Hz, 2H), 3.08 – 3.02 (m, 2H), 2.20 – 2.15 (m, 2H), 1.67 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ = 185.3, 150.7 (2C), 150.5, 140.6, 136.4, 129.1, 128.5 (2C), 123.6, 122.8, 119.9, 115.6, 107.6, 84.2, 69.6, 39.3, 28.3 (3C), 24.5; **MS (ESI) *m/z* (%):** 254 (100), 354 (10) [M^++H], 376 (9) [M^++Na]. **HRMS Calcd for** $C_{21}H_{24}NO_4$ 354.1699, found 354.1710 [M^++H].

Signals for **223: ^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.15 (d, *J* = 8.3 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.16 – 7.07 (m, 2H), 6.97 – 6.93 (d, *J* = 10.0 Hz, 2H), 6.37 – 6.33 (d, *J* = 10.0 Hz, 2H), 3.36 – 3.31 (t, *J* =

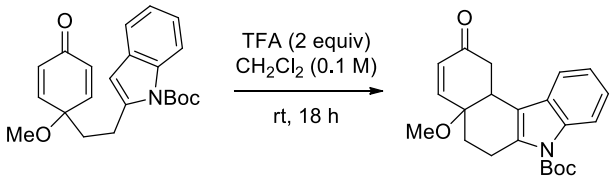
7.1 Hz, 2H), 2.70 – 2.66 (t, *J* = 7.1 Hz, 2H), 1.68 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 185.92, 153.15 (2C), 149.53, 144.96, 139.95, 127.96 (2C), 124.89, 123.79, 123.03, 122.54, 117.59, 115.92, 99.98, 83.96, 47.66, 40.07, 28.24 (3C); **MS (ESI) *m/z* (%):** 280 (100), 336 (48) [M^++H]. HRMS Calcd for $C_{21}H_{22}NO_3$ 336.1594, found 336.1610 [M^++H].

Procedures for the synthesis of derivative *tert*-butyl 4a-methoxy-2-oxo-4a,5,6,11c-tetrahydro-1H-benzo[*c*]carbazole-7(2H)-carboxylate (227)



227

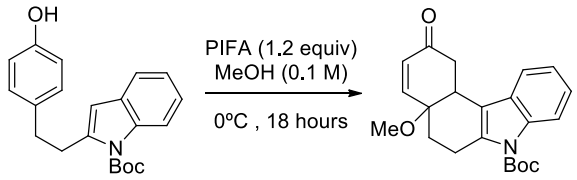
Procedure 1:



221 **227**

To a solution of **221** (18 mg, 0.05 mmol) in CH_2Cl_2 (0.5 ml) at rt was added TFA (8 µl, 0.1 mmol) and the mixture was stirred at rt for 18 hours. The residue is dissolved in CH_2Cl_2 and washed with $NaHCO_3$ sat. The resulting organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 6:1) to afford **227** as a yellow oil (7.5 mg, 40% yield).

Procedure 2:



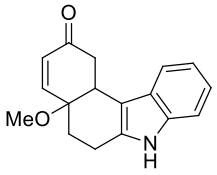
211 **227**

To a solution of **211** (128 mg, 0.38 mmol) in MeOH (3.8 ml) at 0°C was added PIFA (196 mg, 0.45 mmol) and the mixture was stirred at 0°C for 18 hours. MeOH is evaporated under reduced pressure and the residue is dissolved in CH_2Cl_2 and washed with $NaHCO_3$ sat. The resulting organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product

was purified by flash column chromatography (eluent Hex:AcOEt 6:1) to afford **227** as a yellow oil (60.5 mg, 44% yield).

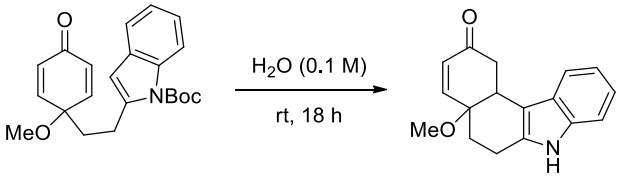
Signals for **227**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.16 – 8.13 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.39 (d, *J* = 7.6 Hz, 1H), 7.29 – 7.19 (m, 2H), 6.96 – 6.92 (d, *J* = 10.3 Hz, 1H), 6.22 – 6.18 (dd, *J* = 10.3 and 1.3 Hz, 1H), 3.85 – 3.79 (dd, *J* = 13.4, 4.9 Hz, 1H), 3.25 (s, 3H), 3.25 – 3.08 (m, 3H), 2.45 – 2.35 (dd, *J* = 16.8, 13.2 Hz, 1H), 2.19 – 2.01 (m, 2H), 1.68 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 197.9, 154.5, 150.5, 136.2, 134.4, 131.5, 128.2, 123.7, 122.6, 117.1, 115.8, 115.8, 83.7, 74.4, 50.8, 43.3, 33.3, 28.7 (3C), 28.3, 22.6; **MS (ESI) *m/z* (%):** 79 (100), 368 (75) [M^++H], 385 (26) [M^++NH_4], 390 (17) [M^++Na]. **HRMS Calcd for** $C_{22}H_{26}NO_4$ 368.1856, found 368.1871 [M^++H].

Procedures for the synthesis of derivative 4a-methoxy-5,6,7,11c-tetrahydro-1H-benzo[*c*]carbazol-2(4aH)-one (228)



228

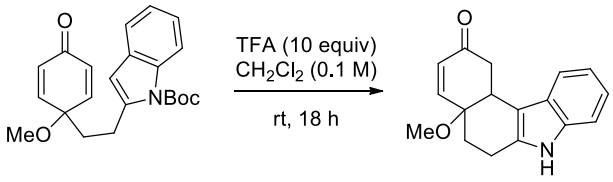
Procedure 1:[142]



221 **228**

A solution of **221** (66 mg, 0.18 mmol) in water (1.8 ml) was heated at 100°C for 18 hours. After cooling to rt, CH_2Cl_2 was added to residue and the resulting organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 6:1) to afford **228** as a brown oil (41.8 mg, 80% yield).

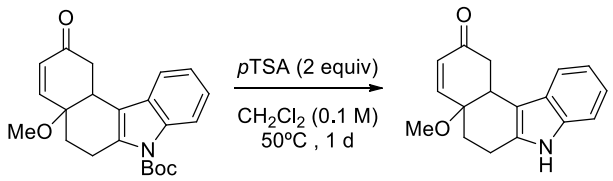
Procedure 2:



221 **228**

To a solution of **221** (46 mg, 0.125 mmol) in CH_2Cl_2 (1.2 ml) was added TFA (0.1 ml, 1.25 mmol) and the mixture was stirred at rt for 18 hours. The residue is dissolved in CH_2Cl_2 and washed with $NaHCO_3$ sat. The resulting organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 6:1) to afford **228** as a brown oil (25 mg, 70% yield).

Procedure 3:

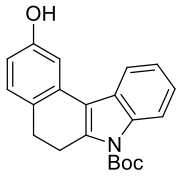


227 **228**

To a solution of **227** (18 mg, 0.05 mmol) in CH_2Cl_2 (0.5 ml) was added TSA (20 mg, 0.1 mmol) and the mixture was stirred at 50°C for 1 day. The residue is dissolved in CH_2Cl_2 and washed with $NaHCO_3$ sat. The resulting organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 6:1) to afford **228** as a brown oil (7.3 mg, 40% yield).

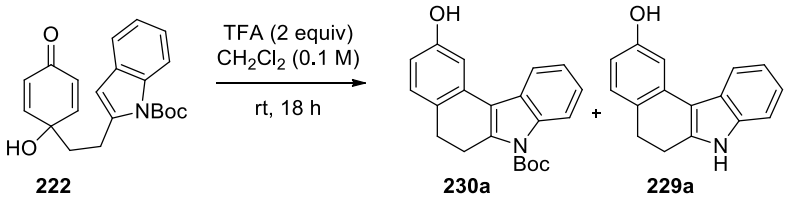
Signals for **228**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.85 (s, 1H), 7.48 – 7.46 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.30 (d, *J* = 8.0 Hz, 1H), 7.17 – 7.07 (m, 2H), 6.92 – 6.89 (d, *J* = 10.4 Hz, 1H), 6.22 – 6.18 (d, *J* = 10.4 Hz, 1H), 3.94 – 3.88 (dd, *J* = 13.1 and 4.7 Hz, 1H), 3.24 (s, 3H), 3.17 – 3.02 (m, 2H), 2.79 – 2.71 (m, 1H), 2.48 – 2.38 (dd, *J* = 16.9 and 13.1 Hz, 1H), 2.13 – 2.09 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 198.6, 154.7, 136.1, 132.6, 131.4, 126.6, 121.4, 119.5, 117.4, 110.7, 110.0, 75.1, 50.9, 44.0, 33.2, 28.6, 19.8; MS (ESI) *m/z* (%):268 (87) [M^++H], 290 (100) [M^++Na], 557 (22) [2M^++Na]. HRMS Calcd for $C_{17}H_{17}NO_2Na$ 290.1151, found 290.1158 [M^++Na].

Procedure for the synthesis of derivative *tert*-butyl 2-hydroxy-5H-benzo[*c*]carbazole-7(6H)-carboxylate (230a)



230a

Procedure:



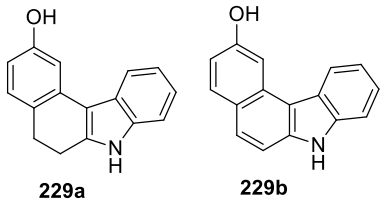
222 **230a** **229a**

81:19 **(230a/229a)**

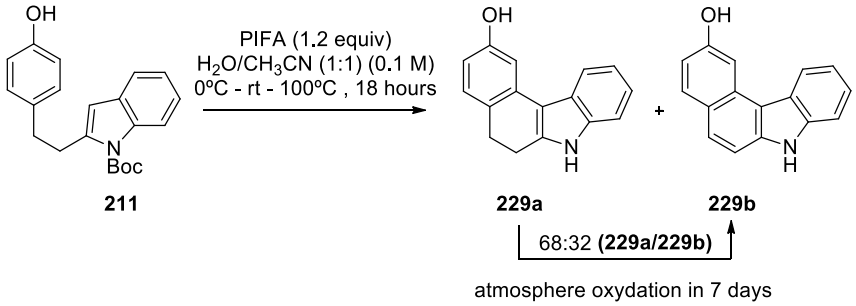
To a solution of **222** (63.5 mg, 0.18 mmol) in CH_2Cl_2 (1.8 ml) at rt was added TFA (27 µ, 0.36 mmol) and the mixture was stirred at rt for 24 hours. When the starting material was consumed, a saturated solution of $NaHCO_3$ was added and extracted with CH_2Cl_2 (3 x 2 ml). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure affording a 81:19 mixture of **230a/229a**. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 5:1 to 3:1) to afford **230a** as a dark brown oil (30.3 mg, 50% yield) and **229a** as brown oil (7.6 mg, 18% yield).

Signals for **230a**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.24 – 8.21 (m, 1H), 8.01 – 7.98 (m, 1H), 7.42 – 7.41 (d, *J* = 2.5 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.13 – 7.11 (d, *J* = 8.0 Hz, 1H), 6.68 – 6.65 (dd, *J* = 8.0 and 2.5 Hz, 1H), 3.32 – 3.27 (t, *J* = 7.7 Hz, 2H), 2.97 – 2.92 (t, *J* = 7.7 Hz, 2H), 1.71 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 154.5, 150.4, 138.9, 136.6, 133.3, 128.5, 126.6, 123.5, 123.1, 119.2, 116.0, 115.7, 112.1, 110.6, 84.2, 28.7, 28.4, 28.3 (3C), 23.8; **MS (FAB) *m/z* (%):** 154 (100), 335 (22) [M^+]. **HRMS Calcd for** $C_{21}H_{21}NO_3$ 335.1521, found 335.1525 [M^+].

Procedure for the synthesis of derivative 6,7-dihydro-5H-benzo[*c*]carbazol-2-ol (229a) and 7H-benzo[c]carbazol-2-ol (229b)

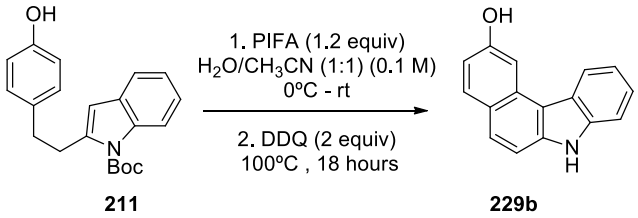


Procedure 1:



To a solution of **211** (75 mg, 0.22 mmol) in a 1:1 mixture of H_2O/CH_3CN (2.2 ml/ 2.2 ml) at 0°C was added PIFA (142 mg, 0.33 mmol) and the mixture was stirred at 0°C for 10 minutes. When the starting material **x** is consumed, the reaction mixture was heated at 100°C for 18 hours. After cooling the reaction mixture to rt, a saturated solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 x 5 ml). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to afford a 70:30 mixture of **229a**/**229b**. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 3:1) to afford a 67:33 mixture of **229a/229b** which completely oxidized after 7 days giving **229b** as a dark brown oil (13 mg, 25% yield).

Procedure 2:



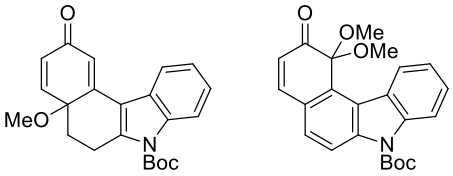
To a solution of **211** (300 mg, 0.89 mmol) in a 1:1 mixture of H_2O/CH_3CN (4.5 ml/ 4.5 ml) at 0°C was added PIFA (572 mg, 1.33 mmol) and the mixture was stirred at 0°C for 10 minutes. DDQ (404 mg, 1.78 mmol) was added and the mixture was heated at 100°C for 18 hours. After

cooling the reaction mixture to rt, a saturated solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 x 5 ml). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent Hex:AcOEt 2:1) to afford **229b** as a dark brown oil (9.6 mg, 5% yield).

Signals for **229a**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.04 (bs, 1H), 8.01 – 7.98 (m, 1H), 7.37 – 7.34 (m, 2H), 7.22 – 7.18 (m, 2H), 7.11 – 7.08 (d, *J* = 8.1 Hz, 1H), 6.57 – 6.54 (dd, *J* = 8.0 and 2.6 Hz, 1H), 3.18 – 2.79 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 154.6, 137.8, 136.1, 135.1, 128.7, 125.5, 124.8, 121.5, 120.6, 119.3, 111.1, 110.5, 109.7, 28.6, 28.3, 22.8; **MS (ESI) *m/z* (%):** 236 (100) [M^++H], 149 (25), 471 (8) [2M^++H]. **HRMS Calcd for** $C_{16}H_{14}NO$ 236.1069, found 236.1076 [M^++H].

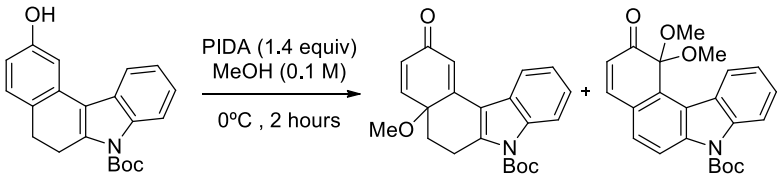
Signals for **229b**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.50 – 8.47 (d, *J* = 7.8 Hz, 1H), 8.40 (bs, 1H), 8.10 – 8.09 (d, *J* = 2.5 Hz, 1H), 7.91 – 7.88 (d, *J* = 8.7 Hz, 1H), 7.80 – 7.77 (d, *J* = 8.7 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.50 – 7.47 (d, *J* = 8.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.08 – 7.04 (dd, *J* = 8.8 and 2.5 Hz, 1H), 5.16 (bs, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ = 154.6, 138.4, 137.7, 131.2, 131.1, 127.3, 124.4, 124.1, 124.1, 121.6, 120.2, 114.6, 114.0, 111.0, 110.2, 106.5; **MS (EI) *m/z* (%):** 204 (22), 233 (100) [M^+]. HRMS Calcd for $C_{16}H_{11}NO$ 233.0841, found 233.0842 [M^+].

Procedure for the synthesis of derivatives *tert*-butyl-4a-methoxy-2-oxo-5,6-dihydro-2H-benzo[*c*]carbazole-7(4aH)-carboxylate (231) and *tert*-butyl 1,1-dimethoxy-2-oxo-1H-benzo[*c*]carbazole-7(2H)-carboxylate (232)



231 **232**

Procedure:



230a **231** **232**

67:33 **(231/232)**

To a solution of **230a** (30 mg, 0.09 mmol) in MeOH (0.9 ml) at 0°C was added PIDA (43.2 mg, 0.13 mmol) and the mixture was stirred at 0°C for 2 hours. MeOH was evaporated under reduced pressure to afford a 67:33 mixture of **231/232**(ortoacetal). The crude product was purified by flash column chromatography (eluent Hex:AcOEt 5:1) to afford **231** as an orange oil (7 mg, 22% yield) and **232** as a brown oil (7.3 mg, 21%).

Signals for **231**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.23 – 8.20 (m, 1H), 7.86 – 7.83 (m, 1H), 7.36 – 7.32 (m, 2H), 6.89 – 6.88 (d, *J* = 1.8 Hz, 1H), 6.67 – 6.64 (d, *J* = 10.1 Hz, 1H), 6.51 – 6.47 (dd, *J* = 10.0 and 1.8 Hz, 1H), 3.53 – 3.41 (m, 1H), 3.33 – 3.25 (dd, *J* = 18.7 and 6.3 Hz, 1H), 3.01 (s, 3H), 2.43 – 2.36 (dd, *J* = 13.7 and 5.8 Hz, 1H), 2.04 – 1.91 (m, 1H), 1.70 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 186.0, 150.3, 149.9, 147.3, 142.1, 136.9, 131.9, 125.9, 124.5, 123.7, 122.44, 119.3, 115.9, 113.4, 85.0, 70.5, 52.0, 34.0, 28.2 (3C), 22.6; **MS (ESI) *m/z* (%):** 366 (100) [M^++H], 310 (62), 731 (24) [2M^++H]; HRMS Calcd for $C_{22}H_{24}NO_4$ 366.1699, found 366.1708 [M^++H].

Signals for **232**: **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 8.94 – 8.91 (d, *J* = 8.2 Hz, 1H), 8.57 – 8.54 (d, *J* = 8.6 Hz, 1H), 8.32 – 8.29 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.43 – 7.35 (m, 2H), 6.28 – 6.25 (d, *J* = 8.7 Hz, 1H), 3.23 (s, 6H), 1.78 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 195.5, 150.7, 147.1, 141.5, 139.6, 132.6, 128.9, 127.9, 127.5, 127.2, 126.4, 124.0, 123.9, 123.2, 117.5, 115.3, 95.6, 84.8, 51.3 (2C), 28.4 (3C); **MS (ESI) *m/z* (%):** 362 (100), 306 (96), 809 (30) [2M^++Na], 416 (14) [M^++Na]; HRMS Calcd for $C_{23}H_{23}NO_5Na$ 416.1468, found 416.1472 [M^++Na].

Facultad de Ciencias

Departamento de Química Orgánica

Utilidad sintética de los p-quinoles: Reacciones de adición conjugada de tipo hetero-Michael y Friedel-Crafts

TESIS DOCTORAL

Carolina García García

Madrid, Diciembre 2014

El desarrollo de nuevos métodos sintéticos que permitan el acceso de manera eficiente y elegante a moléculas con gran interés biológico y estructural, es un objetivo prioritario en el campo de la química orgánica moderna. Los nuevos procesos descritos deben cumplir ciertos requisitos incluyendo generalidad, alta reactividad y productividad, esenciales para futuras aplicaciones efectivas, prácticas y escalables. Una vez establecida la metodología, su aplicación a la síntesis de productos naturales y moléculas de interés biológico tiene un gran impacto en Biología y Medicina.[i]

La estructura de *p*-quinol (4-alquil-4-hidroxi-2,5-ciclohexadienona) se encuentra ampliamente distribuida en la naturaleza tanto en estructuras simples[ii] como más complejas.[iii] Algunas de ellas muestran un amplio abanico de propiedades biológicas interesantes tales como antitumorales,[iv] y tripanocidas.[v] Se cree que su actividad antitumoral es debida al doble sistema de acceptor de Michael, que facilita la interacción con proteínas mediante la formación de enlaces covalentes y da lugar a sistemas altamente funcionalizados.[vi,vii] Los *p*-quinoles diferentemente sustituidos y algunos de sus derivados son importantes estructuras que han sido utilizadas por numerosos grupos de investigación como reactivos de partida en la síntesis de distintos productos naturales.[viii,ix] El grupo hidroxilo en la posición C-4 presenta alta nucleofilia que aumenta la utilidad sintética de estos derivados, pudiéndose comportar como sistemas ambivalentes: nucleófilos por el OH en C-4 y electrófilos gracias a su sistema de doble aceptor de Michael.[x] La presencia de un centro proquiral en C-4 en *p*-quinoles simétricamente sustituidos supone un reto en el desarrollo de reacciones estereoselectivas. De hecho, la desimetrización del fragmento de 2,5-ciclohexadienona se ha convertido en un área de investigación muy activa.[xi] Todas estas características hacen de los *p*-quinoles estructuras únicas para el desarrollo de reacciones dominó o multicomponentes,[xii] para la elaboración de moléculas más complejas.

Entre los numerosos métodos desarrollados para la síntesis de *p*-quinoles[vi] la oxidación de *p*-alquil fenoles es el método más frecuentemente utilizado. Reactivos de iodo (III) hipervalente[xiii] como el PIDA (diacetato de iodobenceno) o el PIFA (bis(trifluoroacetato) de iodobenceno) dan acceso directo a los *p*-quinoles en presencia de agua o alcoholes. Otros oxidantes, como el oxígeno singlete ($^1O_2$), generado o bien por irradiación del oxígeno gaseoso con luz ultravioleta en presencia de fotosensibilizadores[xiv] o por descomposición de Oxono® (trabajo desarrollado por nuestro grupo de investigación),[xv] o H_2O_2[xvi] permiten la síntesis de *p*-peroxi quinoles, los cuales son fácilmente reducidos a *p*-quinoles.

En esta Tesis Doctoral se ha llevado a cabo un estudio de la reactividad de quinoles diferentemente sustituidos en dos tipos de reacciones, con el fin de obtener estructuras altamente funcionalizadas que presentan un enorme interés sintético así como posiblemente propiedades de interés biológico.

El trabajo se presenta dividido en dos grandes capítulos, asociado a los dos tipos de reacciones estudiados:

1. Estudio de reacciones catalizadas por base de *p*-quinoles con aldehídos e iminas.

2. Estudio de la reacción de Friedel-Crafts con *p*-quinoles con diferentes derivados heteroaromáticos.

Estudio de reacciones catalizadas por base de *p*-quinoles con aldehídos e iminas.

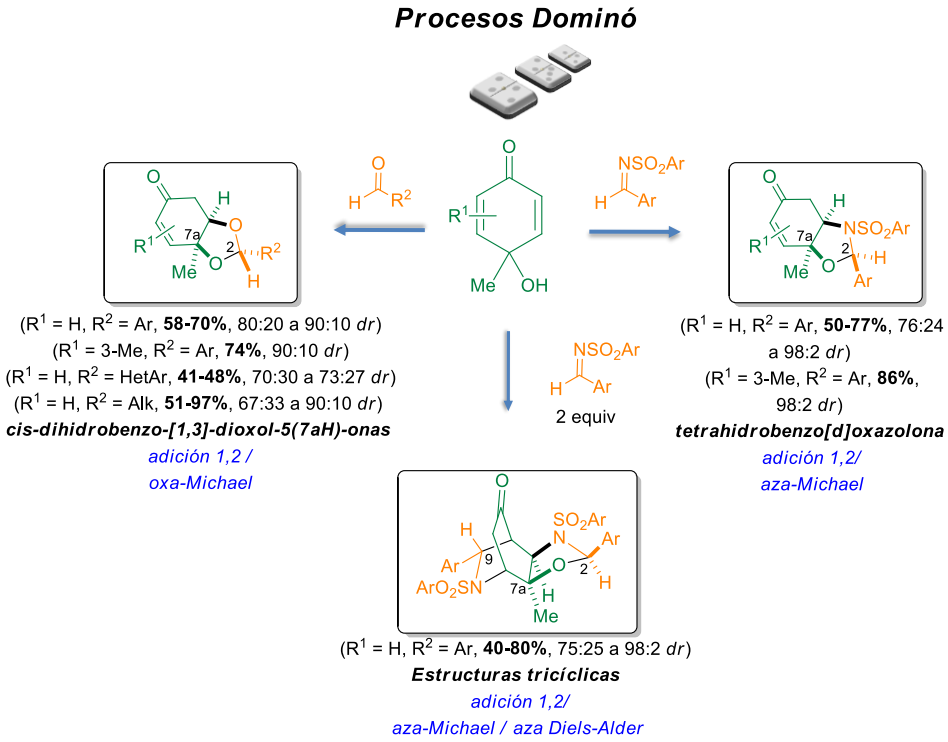
El estudio del comportamiento de los *p*-quinoles en reacciones catalizadas por una base con aldehídos e iminas permitió establecer las siguientes conclusiones:

a) La reacción de *p*-quinoles con aldehídos aromáticos y heteroaromáticos en presencia de 15 mol% de DMAP como base en CH_2Cl_2 como disolvente, dio lugar, de manera diastereoselectiva, a los derivados de *cis*-dihidrobenzo-[1,3]-dioxol-5(7a*H*)-ona con buenos rendimientos y diastereoselectividades (**Esquema 1**).

b) La reacción de *p*-quinoles con aldehídos alifáticos dio lugar a los derivados de *cis*-dihidrobenzo-[1,3]-dioxol-5(7a*H*)-ona con buena diastereoselectividad y rendimiento cuando se utilizó un ácido fosfórico como catalizador en CH_2Cl_2 como disolvente. El mecanismo de reacción propuesto tanto en el caso de los aldehídos aromáticos y heteroaromáticos como los alifáticos consistía en una adición 1,2 del grupo OH del p-quinol sobre el carbono carbonílico del aldehído, seguida de una adición de oxa-Michael intramolecular sobre uno de los dos dobles enlaces de la ciclohexadienona. La estructura del diastereoisómero mayoritario fue confirmada por difracción de RX y permitió evidenciar la fusión *cis* y la relación *cis* existente entre el Me en C-7a y el grupo arilo, heteroarilo o alquilo en C-2. Mediante el uso de técnicas espectroscópicas de resonancia magnética nuclear de ^1H, se pudo concluir que en la estructura del diastereoisómero minoritario, el Me en C-7a y el resto

arilo, heteroarilo o alquilo mantenían una disposición relativa *trans*. Por tanto, el diastereoisómero minoritario es el epímero del mayoritario en C-2 (**Esquema 1**).

c) La reacción de *p*-quinoles con sulfonil aril iminas catalizada por una base, dio lugar a estructuras poliheterobicíclicas o tricíclicas en función de la base y las condiciones utilizadas. Así pues, cuando el sistema catalítico estaba compuesto por 15 mol% de DMAP en CH_2Cl_2 como disolvente, se obtuvieron derivados de tetrahidrobenzo[*d*]oxazolona. El uso de 15 mol% de DABCO junto con 70 mol% de $LiClO_4$ como aditivo en THF como disolvente, permitió el acceso diastereoselectivo a estructuras tricíclicas que contenían un fragmento de piperidina y un fragmento de oxazolidina. El mecanismo de reacción propuesto para la formación de dichas estructuras comenzaría, por la adición 1,2 del OH del *p*-quinol sobre el carbono imínico, seguida por una adición aza-Michael intramolecular sobre uno de los dos dobles enlaces del fragmento de ciclohexadienona. En el caso de la catálisis con DABCO/ $LiClO_4$/THF, el enolato resultante tras la adición de aza-Michael intramolecular se comportaría como un dieno en una reacción de aza Diels-Alder con otra molécula de imina que actúa como dienófilo dando lugar a las estructuras poliheterotricíclicas con buena diastereoselectividad y rendimientos. La estructura del diastereoisómero mayoritario del derivado bicíclico de tetrahidrobenzo[*d*]oxazolona fue determinada por difracción de RX. En ella se observaba la fusión *cis* del biciclo y la relación *trans* entre el Me en C-7a y el resto arilo en C-2. La estructura del diastereoisómero minoritario se elucidó gracias a resonancia magnética nuclear de ^1H, siendo éste epímero del diastereoisómero mayoritario en C-2. La difracción de RX del derivado tricíclico mostró la misma relación *trans* entre el Me en C-7a y el resto arilo en C-2 y una relación cis entre el Me en C-7a y el resto arilo en C-9 correspondiente a la segunda imina. Mediante RMN-^1H se determinó que la estructura del diastereoisómero minoritario cambiaba su configuración en C-9 siendo epímeros en dicho carbono (**Esquema 1**).



Esquema 1

Estudio de la reacción de Friedel-Crafts de *p*-quinoles con diferentes derivados heteroaromáticos.

En el estudio de estas reacciones llevado a cabo en este trabajo, se ha podido establecer que los *p*-quinoles pueden actuar como electrófilos en reacciones de alquilación de Friedel-Crafts de derivados heteroaromáticos, obteniéndose de manera diastereoselectiva, los productos de adición conjugada sobre el fragmento de 2,5-ciclohexadienona.

El estudio de estas reacciones se llevó a cabo de manera inter e intramolecular dando lugar a diferentes derivados de gran interés estructural.

Del estudio intermolecular de la reacción de FC de *p*-quinoles con derivados heteroaromáticos se pueden sacar las siguientes conclusiones:

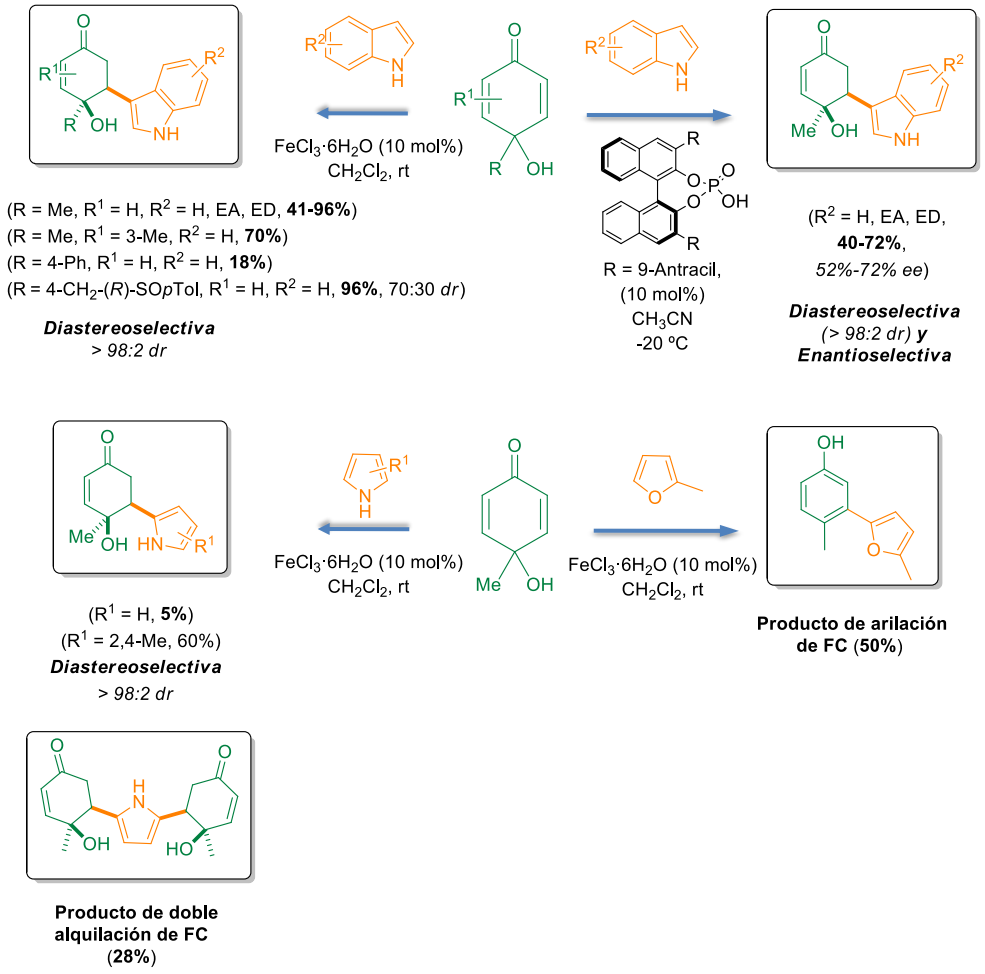
- En la versión racémica estudiada de la alquilación de FC de indoles con *p*-quinoles, la adición conjugada se produce de forma totalmente diastereoselectiva (>98:2 *rd* (relación diastereomérica)), exclusivamente por la cara del quinol que contiene el grupo hidroxilo (**Esquema 2**).

- El sistema catalítico que permite la obtención del producto de adición conjugada con mejores rendimientos está compuesto por 10 mol% de $FeCl_3 \cdot H_2O$ en CH_2Cl_2 como disolvente (**Esquema 2**).

- El uso de indoles diferentemente sustituidos tanto con sustituteyentes electrón atractores (EA) como electrón donadores (ED) da lugar a buenos rendimientos de los productos de alquilación (41-96%) obteniéndose como diastereoisómero mayoritario el que dispone en *cis* el grupo hidroxilo y el fragmento de indol. *p*-Quinoles diferentemente sustituidos (R = Me, R1 = H 3-Me or R = 4-Ph, 4-CH_2SO*p*Tol with R^1 = H) también dan acceso a los productos de alquilación con excelente diastereoselectividad y rendimientos. En cambio, la reacción de los *p*-quinoles con pirroles no se ha podido generalizar, obteniéndose sólo en dos casos el producto de alquilación y en el caso del pirrol no sustituido mayoritariamente el producto de doble alquilación. El uso de furanos da lugar exclusivamente al producto de arilación, mientras que en la reacción con tiofenos (mucho menos reactivos) no se observó el producto de alquiliación de FC (**Esquema 2**).

- El uso de un ácido fosfórico enantiopuro derivado del BINOL que contiene dos restos antracenilo, permitió la obtención de moderados a buenos rendimientos y excesos enatioméricos de entre 52% y 72% en los productos de alquilación de FC de diferentes indoles con la 4-hidroxi-4-metil-2,5-ciclohexadienona (**Esquema 2**).

FC Intermolecular



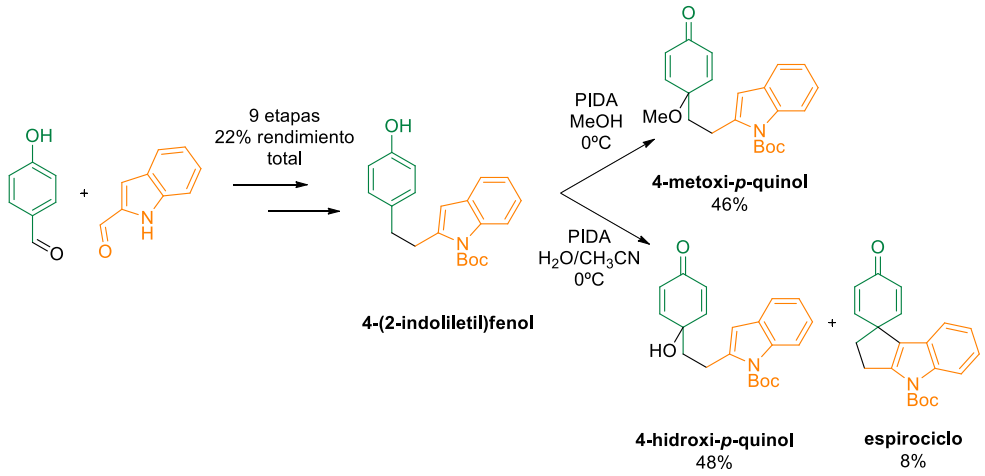
Esquema 2

Los buenos resultados obtenidos en la reacción de Friedel-Crafts intermolecular entre diferentes *p*-quinoles e indoles sugerían la posibilidad de sintetizar derivados de quinol que tuvieran anclados en la posición *orto* o en la *para*, un resto de indol que pudiera adicionarse de manera intramolecular al resto de ciclohexadienona en las condiciones adecuadas. Las reacciones de alquilación intramolecular de tipo Friedel-Crafts de estos compuestos permitirían acceder a estructuras tetracíclicas, difícilmente accesibles de forma directa aplicando otros procedimientos sintéticos. De este estudio se pudieron obtener las siguientes conclusiones:

- El derivado de 4-(2-indoliletil)fenol, precursor de los quinoles necesarios para este estudio, se obtuvo mediante una síntesis de 9 etapas con un 22% de rendimiento

global, a partir de sustratos de partida comerciales 4-hidroxibenzaldehído y 2-indol carboxaldehído (**Esquema 3**).

- La oxidación del 4-(2-indoliletil)fenol con PIDA en MeOH condujo al 4-metoxi derivado de *p*-quinol en un 46% de rendimiento. El 4-hidroxi derivado análogo se obtuvo por oxidación con PIDA en presencia de H_2O, con un 48% de rendimiento. En este último caso se generó un 8% del espirociclo resultante en la adición intramolecular del fragmento de indol del fenol de partida durante la oxidación (**Esquema 3**).

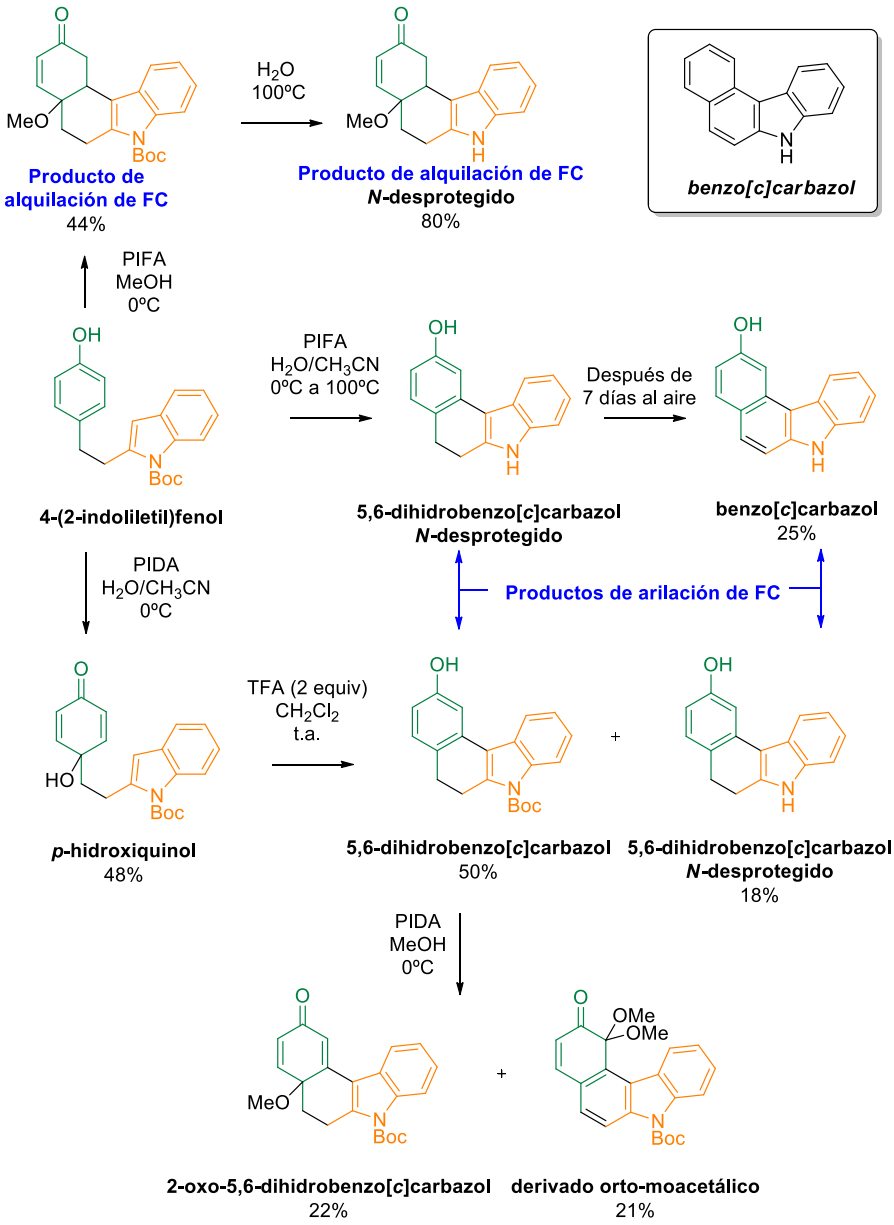


Esquema 3

- A partir de los *p*-quinol derivados se llevó a cabo un estudio de su reactividad con el fin de obtener selectivamente diferentes derivados con esqueleto de benzo[*c*]carbazol siendo los mejores resultados los expuestos en el **Esquema 4**.

- El tratamiento de 4-(2-indoliletil)fenol con PIFA en MeOH dio lugar al producto de alquilación de FC tetrahydrogenado en un 44% de rendimiento. Este derivado se sometió a reflujo utilizando agua como disolvente y dio lugar a un 80% de rendimiento de su análogo *N*-desprotegido. El derivado 4-(2-indoliletil)fenol fue tratado con PIFA utilizando, esta vez, una mezcla de H_2O/CH_3CN como disolvente a 0°C. Tras calentamiento a 100°C el producto de arilación de FC *N*-desprotegido 5,6-dihidrobenzocarbazol fue obtenido y, tras 7 días de oxidación atmosférica, se observó su transformación al derivado benzo[*c*]carbazol con un 25% de rendimiento tras 4 etapas de reacción (oxidación fenólica, alquilación de FC, enolización-eliminación de H_2O y oxidación del doble enlace). Como se ha mencionado anteriormente, la reacción

del derivado 4-(2-indoliletil)fenol con PIDA en H_2O/CH_3CN como disolvente dio lugar al *p*-hydroxiquinol como producto mayoritario en un 48% de rendimiento. Cuando éste fue tratado con TFA en CH_2Cl_2 dio lugar a una mezcla de productos de arilación de FC, el 5,6-dihidrobenzo[*c*]carbazol *N*-Boc protegido y su análogo desprotegido (50% y 18% rendimiento aislado respectivamente). Con el fin de obtener diferentes estructuras con esqueleto de quinol, el 5,6-dihidrobenzo[*c*]carbazol se trató con PIDA en MeOH obteniéndose una mezcla del 2-oxo-5,6-dihidrobenzo[*c*]carbazol y el derivado orto monoacetálico con un 22% y 21% de rendimiento aislado.



Esquema 4

REFERENCIAS

[i] a) Shu, Y.-Z. "Recent Natural Products Based Drug Development : a Pharmaceutical Industry Perspective". *J. Nat. Prod.* **1998**, *61*, 1053. b) Newman, D. J.; Cragg, G. M.; Snader, K. M. "The Influence of Natural Products upon Drug Discovery". *Nat. Prod. Rep.* **2000**, *17*, 215. c) Nicolaou, K. C.; Vourloumis, D.; Wissinger, N.; Baran, P. S. "The Art and Science of the Total Synthesis at the Dawn of the Twenty-first Century" *Angew. Chem. Int. Ed.* **2000**, *39*, 44.

[ii] Jacaranone: a) Rana, A.; Bhangalia, S.; Singh, H. P. *Nat. Prod. Res*. **2013**, *27*, 1167; Cornoside: b) Taskova, R. M.; Gotfredsen, C. H.; Jensen, S. R. *Phytochemistry*. **2005**, *66*, 1440; c) Guiso, M.; Marra, C.; Piccioni, F.; Nicoletti, M. *Phytochemisrty*. **1997**, *45*, 193; Hallerone and Halleridone: d) Ravikanth, V.; Ramesh, P.; Diwan, P. V.; Venkateswarlu, Y. *Biochem. Syst. Ecol*. **2000**, *28*, 905.

[iii] Tetrapetalones: a) Komoda, T.; Yoshida, K.; Abe, N.; Sugiyama, Y.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 104; Frondosin C: b) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewiz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047; Elisabethol: c) Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215; Coproverdine: d) Urban, S.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2002**, *65*, 1371.

[iv] a) Massaoka, M. H.; Matsuo, A. L.; Figueiredo, C. R.; Farias, C. F.; Girola, N.; Arruda, D. C.; Scutti, J. A. B.; Romoff, P.; Favero, O. A.; Ferreira, M. J. P.; Lago, J. H. G.; Travassos, L. R. *PLoS One*. **2012**, *7*, 38698, 1; b) Chew, E.-H.; Lu, J.; Bradshaw, T. D.; Holgren, A. *FASEB J.* **2008**, *22*, 2072; c) McCarroll, A.; Bradshaw, T. D.; Westwell, A. D.; Matthews,C. S.; Stevens, M. F. G. *J. Med. Chem.* **2007**, *50*, 1707; d) Berry, J. M.; Bradshaw, T. D.; Fichtner, I.; Ren, R.; Schwalbe, C. H.; Wells, G.; Chew, E.-H.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem*. **2005**, *48*, 639; e) Bradshaw, T. D.; Matthews, C. S.; Cookson, J.; Chew, E.-H.; Shah, M.; Bailey, K.; Monks, A.; Harris, E.; Westwell, A. D., Wells, G.; Laughton, C. A.; Stevens, M. F. G. *Cancer Res.* **2005**, *65*, 3911.

[v] Capes, A.; Patterson, S.; Wyllie, S.; Hallyburton, I.; Collie, I. T.; McCarroll, A. J.; Stevens, M. F. G.; Frearson, J. A.; Wyatt, P. G.; Fairlamb, A. H.; Gilbert, I. H. *Bioorg. Med. Chem.* **2012**, *20*, 1607.

[vi] Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383.

[vii] Para aplicaciones sintéticas de *p*-[(*p*-tolylsulfinyl)methyl]-*p*-quinols ver: a) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Org. Lett.* **2005**, *7*, 1419; b) Carreño, M. C.; Somoza, A.; Ribagorda, M.; Urbano, A. *Chem. Eur. J.* **2007**, *13*, 879; c) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Chem. Eur. J.* **2007**, *13*, 1064; d) Merino, E.; Melo, R. P. A.; Ortega-Guerra, M.; Ribagorda, M.; Carreño, M. C. *J. Org. Chem.* **2009**, *74*, 2824; e) Para un repaso general del trabajo de nuestro grupo de investigación ver: Carreño, M. C.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Comm.* **2009**, 6129.

[viii] a) Thebtaranonth, Ch.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84; b) Balci, M.; Sutbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715; c) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857; d) Wang, X.; Porco, J. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3067; e) Baldwin, J. E.; Adlington, R. M.; Sham, V. W.-W.; Márquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353.

[ix] a) Barradas, S.; Hernández-Torres, G.; Urbano, A.; Carreño, M. C. *Org. Lett.* **2012**, 14, 5952; b) Kim, I.; Kim, K.; Choi, J. *J. Org. Chem*. **2009**, *74*, 8492; b) Barradas, S.; González-López, M.; Latorre, A.; Urbano, A.; Carreño, M. C. *Org. Lett*. **2007**, *9*, 5019.

[x] a) Carreño, M. C.; García Luzón, C.; Ribagorda, M. *Chem. Eur. J.* **2002**, *8*, 208; b) Carreño, M. C.; Ribagorda, M. *Org. Lett.* **2003**, *5*, 2425.

[xi] Para ejemplos de desimetrizaciones catalíticas de ciclohexadienonas ver: a) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552; b) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, 130, 404; c) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056; d) Yuki Fukui, P. L.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin G.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700.

[xii] a) Walji, A. M.; MacMillan, D. W. C. *Synlett.* **2007**, 1477; b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; c) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693; d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem*. **2010**, *2*, 167.

[xiii] a) Moriarty, R. M.; Prakash, O. *Org. React*. **2001**, *57*, 327; b) Parra, A.; Reboredo, S. *Chem. Eur. J.* **2013**, *19*, 17244.

[xiv] DeRosa, M. C., Crutchley, R. J. *Coord. Chem. Rev*. **2002**, 351.

[xv] a) Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem. Int. Ed*. **2006**, *45*, 2737; b) Barradas, S.; Carreño, M. C.; González-López, M., Urbano, A. *Org. Lett*. **2007**, *46*, 5019; c) Barradas, S.; Urbano, A.; Carreño, M. C. *Chem. Eur. J.* **2009**, *15*, 9286.

[xvi] Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *Angew. Chem*. **2005**, *117*, 314; *Angew. Chem. Int. Ed*. **2005**, *44*, 310.